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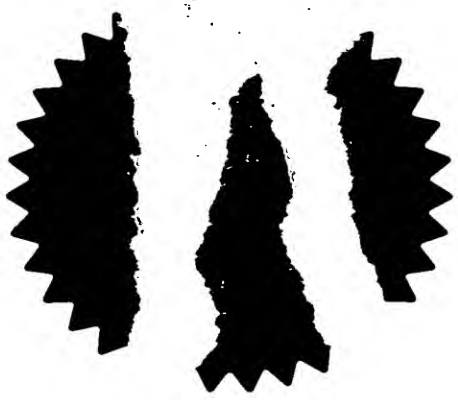

Signed

Dated 7 November 2003

Patents Form 1/77

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20FEB03 E786305-1 D01298
P01/7700 0.00-0303852.8

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

PC25539

2. Patent application number
(The Patent Office will fill in this part)

0303852.8

19 FEB 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ

Patents ADP number *(if you know it)* 6892673001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

TRIAZOLE COMPOUNDS USEFUL IN THERAPY

5. Name of your agent *(if you have one)*

Dr. S.M. Cosway

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

UK Patent Department
Ramsgate Road,
Sandwich, Kent,
CT13 9NJ
United Kingdom

Patents ADP number *(if you know it)* 8466302001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	79
Claim *(s)*	4
Abstract	0
Drawing *(s)*	0

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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature S.M. Cosway

Date 19th February 2003

12. Name and daytime telephone number of person to contact in the United Kingdom — Dr. S.M. Cosway — 01304.643723

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Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

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d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

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Triazole Compounds Useful in Therapy

This invention relates to novel compounds useful in therapy and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

Japanese patent application No. 09328484 describes triazole quinoxalines useful as anti-allergy and anti-inflammatory agents. Japanese patent application No. 09132576 describes triazole quinoxalines useful as anti-allergy and anti-inflammatory agents. Japanese patent application No. 06135965 describes triazole quinoxalines useful for curing and preventing allergies, inflammation and PAF-associated diseases. Japanese patent application No. 06128262 describes triazole quinoxalines useful for intermediates of drugs and agrochemicals.

The compounds of the present invention have been found to have useful pharmaceutical properties. They may be used to treat aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, oedema, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male or female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection or urolithiasis. In particular, they exhibit vasopressin antagonistic activity and can be used in the treatment of dysmenorrhoea.

There is a high unmet need in the area of menstrual disorders and it is estimated that up to 90% of all menstruating women are affected to some degree. Up to 42% of women miss work or other activities due to menstrual pain and it has been estimated that around 600 million work hours a year are lost in the US as a result (costing around $2 billion in lost productivity).

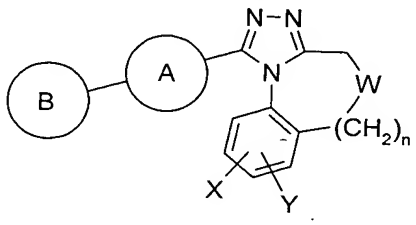
Menstrual pain in the lower abdomen is caused by myometrial hyperactivity and reduced uterine blood flow. These pathophysiological changes result in abdominal pain that radiates out to the back and legs. This may result in women feeling nauseous, having headaches and suffering from insomnia. This condition is called dysmenorrhoea and can be classified as either primary or secondary dysmenorrhoea.

Primary dysmenorrhoea is diagnosed when no abnormality causing the condition is identified. This affects up to 50% of the female population. Where an underlying gynaecological disorder is present, such as endometriosis, pelvic inflammatory disease (PID), fibroids or cancers, secondary dysmenorrhoea will be diagnosed. Secondary dysmenorrhoea is diagnosed in only approximately 25% of women suffering from dysmenorrhoea. Dysmenorrhoea can occur in conjunction with menorrhagia, which accounts for around 12% of referrals to gynaecology outpatients departments.

Currently, women suffering from primary dysmenorrhoea are treated with non-steroidal anti-inflammatory drugs (NSAID's) or the oral contraceptive pill. In cases of secondary dysmenorrhoea surgery may be undertaken to correct the underlying gynaecological disorder.

Women suffering from dysmenorrhoea have circulating vasopressin levels which are greater than those observed in healthy women at the same time of the menstrual cycle. Inhibition of the pharmacological actions of vasopressin, at the uterine vasopressin receptor, may prevent dysmenorrhoea.

According to the present invention there is provided a compound of formula **(I)**,



(I)

W is O, S, or NR^1

R^1 represents H, C_{1-6} alkyl, $-(CH_2)_a-[C_{3-8}$ cycloalkyl], phenyl, benzyl, pyridyl, pyrimidyl, $-COR^2$, $-CO_2R^2$, $-CO-(CH_2)_a-NR^2R^3$, $-SO_2R^2$, $-(CH_2)_b-OR^2$, $-(CH_2)_b-NR^2R^3$, or a saturated

heterocycle of from 3 to 8 atoms containing one or more heteroatoms selected from O, N and S;

X and Y independently represent H, halogen, OH, CF_3, OCF_3, R^4, $-(CH_2)_d-CONR^4R^5$, $-(CH_2)_d-CN$, $-(CH_2)_d-SO_2NR^4R^5$, $-(CH_2)_d-NR^4SO_2Me$, $-(CH_2)_d-COR^4$, $-(CH_2)_d-OCOR^4$, $-(CH_2)_d-NHCOR^4$, $-(CH_2)_d-NR^4COR^5$, $-(CH_2)_d-OR^6$ or $-(CH_2)_d-CO_2R^6$;

Ring **A** represents a piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl group;

Ring **B** represents a phenyl, pyridinyl or pyrimidinyl group (optionally substituted with one or more groups independently selected from halogen, CN, $CONH_2$, CF_3, OCF_3, R^7, and $-(CH_2)_f-OR^8$);

R^2, R^3, R^4, $R^5$and R^7 independently represent H, straight or branched C_{1-6} alkyl, $-(CH_2)_c-[C_{3-8}$ cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl;
or R^2 and R^3, or R^4 and R^5, together with the nitrogen atom to which they are attached independently represent a heterocycle of from 3 to 8 atoms;

R^6 and R^8 independently represent H, straight or branched C_{1-6} alkyl, $-(CH_2)_c-[C_{3-8}$ cycloalkyl], $-(CH_2)_e-NR^4R^5$, $-(CH_2)_e-OR^4$, phenyl, benzyl, pyridyl or pyrimidyl;

n = 0, 1 or 2;

a , c, d and f are all independently selected from 0, 1, 2 or 3;
b and e are independently selected from 2 or 3.

In the above definitions, halogen means fluoro, chloro, bromo or iodo. Alkyl groups containing the requisite number of carbon atoms, except where indicated, can be unbranched or branched chain. Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Heterocycles included within the definition of "heterocycle" are pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzimidazolyl,

quinazolinyl, phthalazinyl, benzoxazolyl and quinoxalinyl, together with partially or fully saturated versions thereof as well as azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl and morpholinyl.

Preferred groups of compounds are those in which:

(i) W is NR^1;

(ii) W is O;

(iii) R^1 is C_1-C_6 alkyl, and more preferably methyl, i-propyl or n-butyl;

(iv) R^1 is H;

(v) R^1 is $-COR^2$

(vi) R^1 is $-SO_2R^2$

(vii) R^1 is $-CO-(CH_2)_a-NR^2R^3$;

(viii) R^2 is C_1-C_6 alkyl, and more preferably methyl, i-propyl or t-butyl;

(ix) R^2 is $-(CH_2)_c$-[C_3-C_8 cycloalkyl], preferably cyclopropyl;

(x) R^3 is C_1-C_6 alkyl, and more preferably methyl, i-propyl or n-butyl;

(xi) X is H;

(xii) Y is in the 4-position of the aromatic ring to which it is attached;

(xiii) Y is halogen, preferably chloro;

(xiv) ring **A** is linked to ring **B** via a nitrogen atom

(xv) ring **A** is piperidinyl;

(xvi) ring **A** is piperazinyl;

(xvii) ring **B** is pyridinyl, preferably 2-pyridinyl;

(xviii) ring **B** is pyrimidinyl, preferably 2-pyrimidinyl;

(xix) ring **B** is phenyl;

(xx) ring **B** is unsubstituted;

(xxi) n is 1;

(xxii) n is 2.

Preferred compounds according to the present invention are:

1-(3,4,5,6-Tetrahydro-2H- [1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

5-Methyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

1-[1-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-ethanone;

8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

8-Chloro-5-methyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene trihydrochloride;

8-Chloro-5-isopropyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene trihydrochloride;

8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5-(tetrahydro-pyran-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

1-[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-ethanone dihydrochloride;

[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-cyclopropyl-methanone dihydrochloride;

1-[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-2,2-dimethyl-propan-1-one dihydrochloride;

8-Chloro-5-methanesulfonyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

8-Chloro-1-(1-pyrimidin-2-yl-piperidin-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

8-Chloro-5-methyl-1-(1-pyrimidin-2-yl-piperidin-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

8-Chloro-5-isopropyl-1-(1-pyrimidin-2-yl-piperidin-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

8-Chloro-5-methanesulfonyl-1-(1-pyrimidin-2-yl-piperidin-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

[8-Chloro-1- (1-pyrimidin-2-yl-piperidin-4-yl)-4H, 6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-cyclopropyl-methanone;

1-[8-Chloro-1-(1-pyrimidin-2-yl-piperidin-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-2,2-dimethyl-propan-1-one;

1-[8-Chloro-1-(1-pyrimidin-2-yl-piperidin-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-ethanone;

8-Chloro-1-(6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene;

4-(8-Chloro-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulen-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-carbonitrile;

4-(8-Chloro-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulen-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-carboxylic acid amide;

13-Chloro-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-2,4,5,8-tetraaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene;

1-[13-Chloro-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-2,4,5,8-tetraaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaen-8-yl]-ethanone;

13-Chloro-8-methyl-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-2,4,5,8-tetraaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene;

3-(1-Pyrimidin-2-yl-piperidin-4-yl)-8-oxa-2,4,5-triaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene;

8-Chloro-1-(1-pyrimidin-2-yl-piperidin-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene;

13-Chloro-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-8-oxa-2,4,5-triaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene;

3-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-8-oxa-2,4,5-triaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene dihydrochloride;

8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene;

7-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene dihydrochloride;

1-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene;

8-Methoxy-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene dihydrochloride;

8-Fluoro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene;

8,9-Difluoro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene dihydrochloride;

9-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene dihydrochloride;

1-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-8-trifluoromethoxy-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene;

8-Methyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene; and

1-[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-2-dimethylamino-ethanone;

The pharmaceutically acceptable salts of the compounds of formula **(I)** include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate, camsylate, citrate, edisylate, esylate, fumarate, gluceptate, gluconate, glucuronate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, hydrogen phosphate, isethionate, D- and L-lactate, malate, maleate, mesylate, methylsulphate, 2-napsylate, nicotinate, nitrate, orotate, palmoate, phosphate, saccharate, stearate, succinate, sulphate, D- and L- tartrate, and tosylate salts.

Suitable base salts are formed from bases, which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

For a review on suitable salts see Stahl and Wermuth, Handbook of Pharmaceutical Salts: Properties, Selection and Use, Wiley-VCH, Weinheim, Germany (2002).

A pharmaceutically acceptable salt of a compound of formula **(I)** may be readily prepared by mixing together solutions of the compound of formula **(I)** and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Pharmaceutically acceptable solvates in accordance with the invention include the hydrates and solvates wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO .

Also within the scope of the invention are clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in non-stoichiometric amounts. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of formula **(I)** include references to salts thereof and to solvates and clathrates of compounds of formula **(I)** and salts thereof.

The invention includes all polymorphs of compounds of formula **(I)** as hereinbefore defined.

Also within the scope of the invention are so-called "prodrugs" of the compounds of formula **(I)**. Thus certain derivatives of compounds of formula **(I)** which have little or no pharmacological activity themselves can, when metabolised upon administration into or onto the body, give rise to compounds of formula **(I)** having the desired activity. Such derivatives are referred to as "prodrugs".

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula **(I)** with certain moieties know to those skilled in the art as "pro-moieties" as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Finally, certain compounds of formula **(I)** may themselves act as prodrugs of other compounds of formula **(I)**.

Compounds of formula **(I)** containing one or more asymmetric carbon atoms can exist as two or more optical isomers. Where a compound of formula **(I)** contains an alkenyl or alkenylene group, geometric *cis/trans* (or Z/E) isomers are possible, and where the compound contains, for example, a keto or oxime group, tautomeric isomerism ('tautomerism') may occur. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all optical isomers, geometric isomers and tautomeric forms of the compounds of formula **(I)**, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, fractional crystallisation and chromatography.

Conventional techniques for the preparation/isolation of individual stereoisomers include the conversion of a suitable optically pure precursor, resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral HPLC, or fractional crystallisation of diastereoisomeric salts formed by reaction of the racemate with a suitably optically active acid or base, for example, tartaric acid.

The present invention also includes all pharmaceutically acceptable isotopic variations of a compound of the formula **(I)**. An isotopic variation is defined as one in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen such as ^{2}H and ^{3}H, carbon such as ^{13}C and ^{14}C, nitrogen such as ^{15}N, oxygen such as ^{17}O and ^{18}O, phosphorus such as ^{31}P and ^{32}P, sulphur such as ^{35}S, fluorine such as ^{18}F and chlorine such as ^{36}Cl.

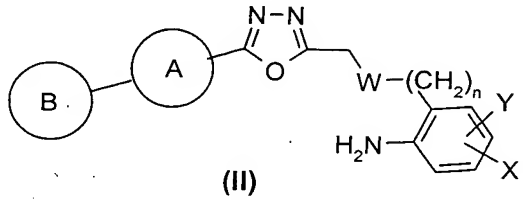
Substitution of the compounds of the invention with isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Certain isotopic variation of the compounds of formula **(I)**, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Isotopic variations of compounds of formula **(I)** can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using appropriate isotopic variations of suitable reagents.

According to the present invention there is also provided a process for the production of a compound of formula **(I)**, which comprises:

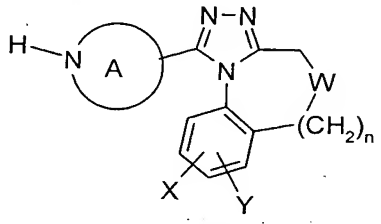
a) reacting a compound of formula **(II)** with an acid catalyst



(II)

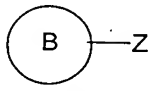
wherein rings A and B, and groups W, X, Y and n are as defined above.

b) reacting a compound of formula **(III)**



(III)

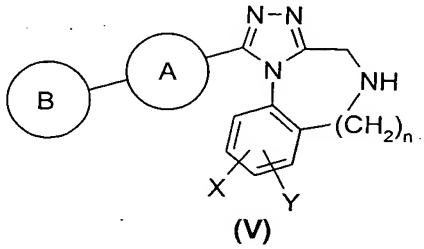
with a compound of formula **(IV)**



(IV)

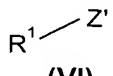
wherein rings A and B, and groups W, X, Y and n are as defined above, and Z represents a leaving group such as halogen.

c) when W in compound **(I)** represents NR^1, reacting a compound of formula **(V)**



(V)

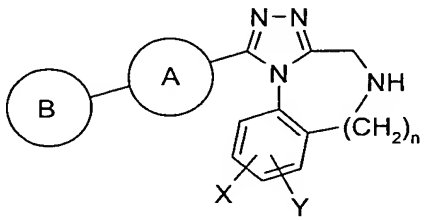
with a compound of formula **(VI)**



(VI)

wherein rings A and B, and groups R^1, X, Y and n are as defined above, and Z' represents a leaving group such as halogen.

d) When W in compound (I) represents NR^1, reacting a compound of formula **(V)**



(V)

with a compound of formula **(VII)**

(VII)

wherein rings A and B, and groups R^1, X, Y and n are as defined above.

Unless otherwise provided herein:

WSCDI means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

DCC means N,N'-dicyclohexylcarbodiimide;

HOAT means 1-hydroxy-7-azabenzotriazole;

HOBT means 1-hydroxybenzotriazole hydrate;

PyBOP® means Benzotriazol-1-yloxytris(pyrrolidino)phosphoniumhexa fluorophosphate;

PyBrOP® means bromo-tris-pyrrolidino-phosphoniumhexafluoro phosphate;

HBTU means O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluoro-phosphate.

Mukaiyama's reagent means 2-chloro-1-methylpyridinium iodide;

KHMDS means potassium bis(trimethylsilyl)amide;

Hünig's base means N-ethyldiisopropylamine;

Et_3N means triethylamine;

NMM means N-methylmorpholine;

HMDS means hexamethyldisilazane

BINAP means 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;

Dba means dibenzylideneacetone;

Boc means *tert*-butoxycarbonyl;

CBz means benzyloxycarbonyl;

p-TSA means *p*-toluenesulphonic acid

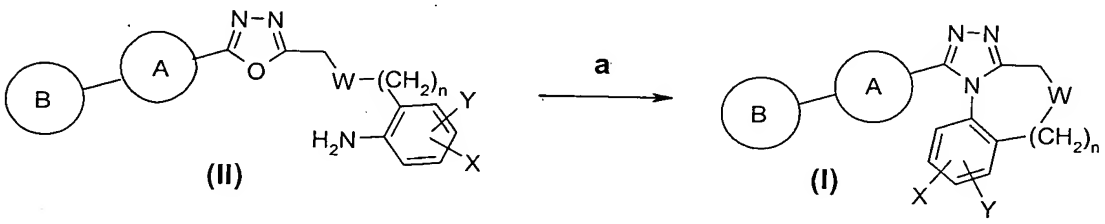
TBAF means tetra-butyl ammonium fluoride

MeOH means methanol, EtOH means ethanol, and EtOAc means ethyl acetate;

THF means tetrahydrofuran, DMSO means dimethyl sulphoxide, and DCM means dichloromethane, DMF means N,N-dimethylformamide, NMP means N-methyl-2-pyrrolidinone;

AcOH means acetic acid, TFA means trifluoroacetic acid.

The following schemes illustrate the preparation of compounds of the formula **(I)**, throughout which Rings A and B, and groups W, X, Y, and n are as defined above unless otherwise stated. **(I')** represents **(I)** when W is NR^1.



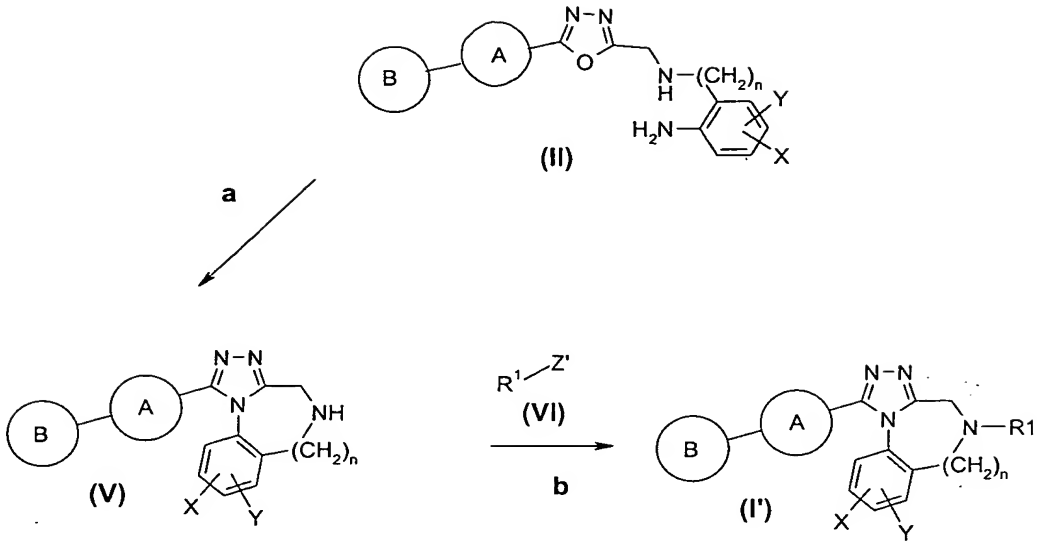
Scheme 1.1

Step (a): Oxadiazole **(II)** is reacted with an acid catalyst to give the compound of formula **(V)**. Typically the reaction is carried out by heating the starting materials to elevated temperatures, such as 100-150°C, for 1 to 48 hours with a suitable acidic catalyst such as p-TSA, or Lewis acid catalyst such as magnesium chloride, optionally using a high boiling solvent such as xylene.

Preferred conditions are:

Amine **(II)** and cat. P-TSA, in xylene at 140°C for 48 hrs.

When W = NR^1, then:



Scheme 1.2

Z' is OH or halo, typically Cl

Compounds suitable for use as compound **(VI)** are commercially available or are known in the literature.

Step (b): The reaction of amine **(V)** with compound **(VI)** can be carried out by standard methods.

When R^1 = COR^2, CO_2R^2, $CO\text{-}(CH_2)_b\text{-}NR^3R^4$, SO_2R^2 then, typically, the coupling may be undertaken by using:

(i) an acyl/sulphonyl/ chloride **(VI)** + amine **(V)** with an excess of acid acceptor, in a suitable solvent; or

(ii) an acid **(VI)** with a conventional coupling agent + amine **(V)**, optionally in the presence of a catalyst, with an excess of acid acceptor in a suitable solvent; and

(iii) when R^1 represents an Aryl group, an aryl halide **(VI)** + amine **(V)**, optionally in the presence of a catalyst, with an excess of acid acceptor in a suitable solvent.

Typically the conditions are as follows:

Acylation/Sulphonylation, Z=Cl

(i) An excess of acyl/sulphonyl chloride **(VI)** (generated in-situ), 1 eq. of amine **(V)**, optionally with an excess of 3° amine such as Et_3N, Hünig's base or NMM, in DCM or THF, without heating for 1 to 24 hrs.

The preferred conditions are:

Amine **(V)**, 1.5 eq. acid/sulphonyl chloride **(VI)**, 1.5 eq. NMM in DCM at rt. for 16 hours.

Amide Bond Formation, Z=OH

(ii) Excess acid **(VI)**, WSCDI /DCC and HOBT/HOAT, 1 eq. of amine **(V)**, with an excess of NMM, Et_3N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 48 hrs; or

excess acid **(VI)**, PYBOP®/PyBrOP®/Mukaiyama's reagent, 1 eq. of amine **(V)**, with an excess of NMM, Et_3N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 24 hrs.

Arylation (R^1 = Aryl, heteroaryl), Z = halo

(iii) Arylation of compound **(V)** can be carried out by a palladium catalysed cross-coupling reaction using a suitable base (*t*-BuONa), a catalytic amount of suitable additive such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and a suitable palladium catalyst in toluene at elevated temp for 1 to 24 hours under an inert atmosphere, to give compound **(I')**. Alternatively compound **(I')** can be prepared by reaction of the amine **(I)** with compound **(VI)** by heating at elevated temperature, such as 50°C-140°C, in a suitable solvent such as DMF, NMP or 1,4-dioxan for about 1-48 hrs with a base such as potassium carbonate, sodium hydrogen carbonate or Hünig's base.

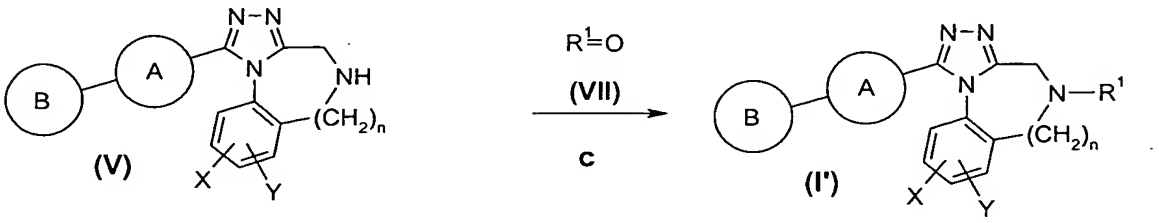
Preferred conditions are:

1-2.5 eq. halide **(VI)**, 1-2 eq. potassium carbonate in N,N-dimethylformamide at 50 °C for 4-18 hours; or

1-2.5 eq. halide **(VI)**, 2-3 eq. Hünig's base, in 1,4-dioxan or NMP at reflux for 18-48 hrs; or

1 eq. Halide **(VI)**, 3.5 eq. NaOt-Bu, 0.08eq BINAP, 0.4 eq. $Pd(dba)_2$, in toluene for 8 hrs at 70°C.

Alternatively, compounds **(I')** may be prepared by the route shown below in **scheme 1.3**.



Scheme 1.3

Compounds suitable for use as compound **(VII)** are commercially available or are known in the literature.

Step (c): Amine **(V)** is reacted with an excess of aldehyde/ketone **(VII)** in the presence of a reducing agent, such as sodium triacetoxy borohydride or sodium cyanoborohydride, to give the compound of formula **(I')**. This reaction may be carried out by:

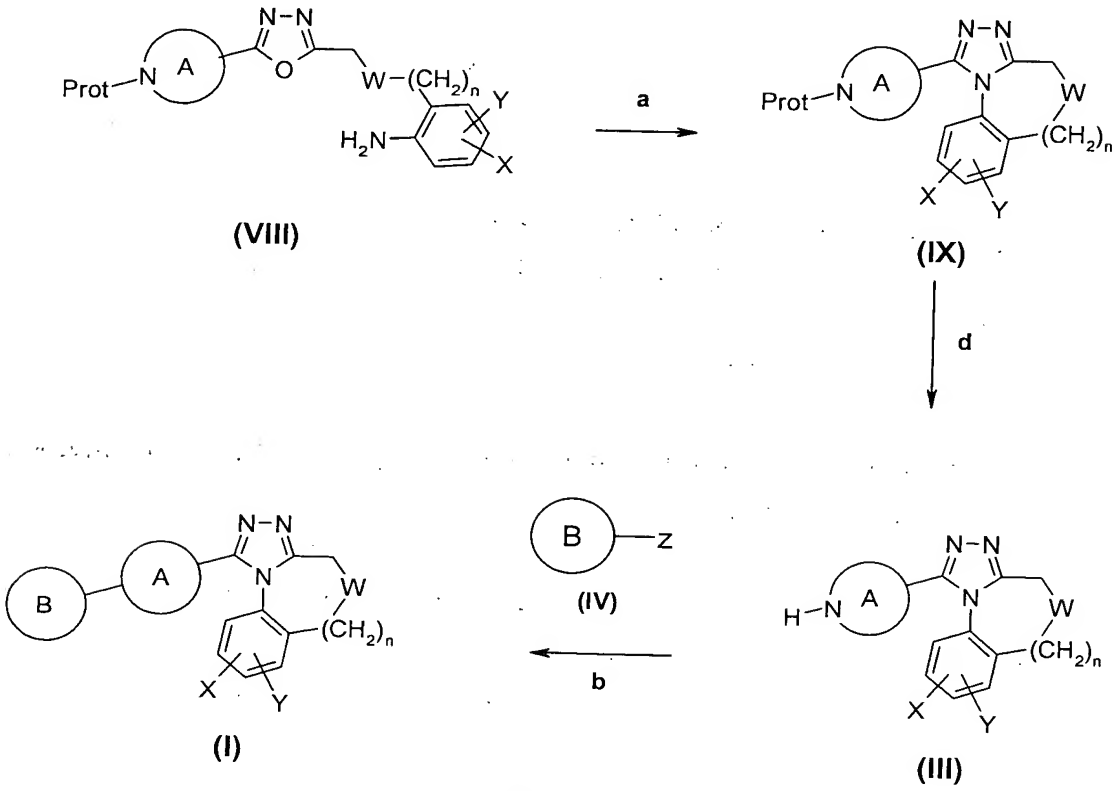
stirring the starting materials at temperatures such as 20°C-80°C for 1 to 48 hours in a suitable solvent such as dichloromethane, or

heating amine **(V)** with excess compound **(VII)** with a suitable Lewis acid catalyst such titanium tetrachloride or titanium tetraisopropoxide at temperatures such as 50°C-100°C in a suitable solvent such as dichloroethane or ethanol for 1-18 hours, followed by reduction of the intermediate imine/iminium species with a suitable reducing agent, such as sodium borohydride, or hydrogenolysis over a suitable catalyst, such as platinum oxide or palladium on carbon.

Preferred conditions are:

Amine **(V)**, 1.5 eq. Aldehyde/ketone **(VII)**, 2.0 eq. sodium triacetoxy borohydride in dichloromethane at room temperature for 2 hours.

When ring B is linked to ring A via an N atom, and W represents O or S then:



Scheme 2.1

Prot represents a suitable protecting group for nitrogen, for example Boc, CBz or Allyl carbamate. Standard methodology for nitrogen protecting groups is used, such as that found in textbooks (e.g. "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz). Z represents a leaving group such as halogen.

Compounds suitable for use as compound **(IV)** are commercially available or are known in the literature.

Arylation of compound **(III)** can be carried out as described in **Step (b)** above.

Preferred conditions are:

1-2.5 eq. halide **(IV)**, 1-2 eq. potassium carbonate in N,N-dimethylformamide at 50 °C for 4-18 hours; or

1-2.5 eq. halide **(IV)**, 2-3 eq. Hünig's base, in 1,4-dioxan or NMP at reflux for 18-48 hrs; or

1 eq. halide **(IV)**, 3.5 eq. NaOt-Bu, 0.08eq BINAP, 0.4 eq. $Pd(dba)_2$, in toluene for 8 hrs at 70°C.

Step (d): Deprotection of compound **(IX)** is undertaken using standard methodology, as described in "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz".

When Prot is Boc, the preferred methods are:

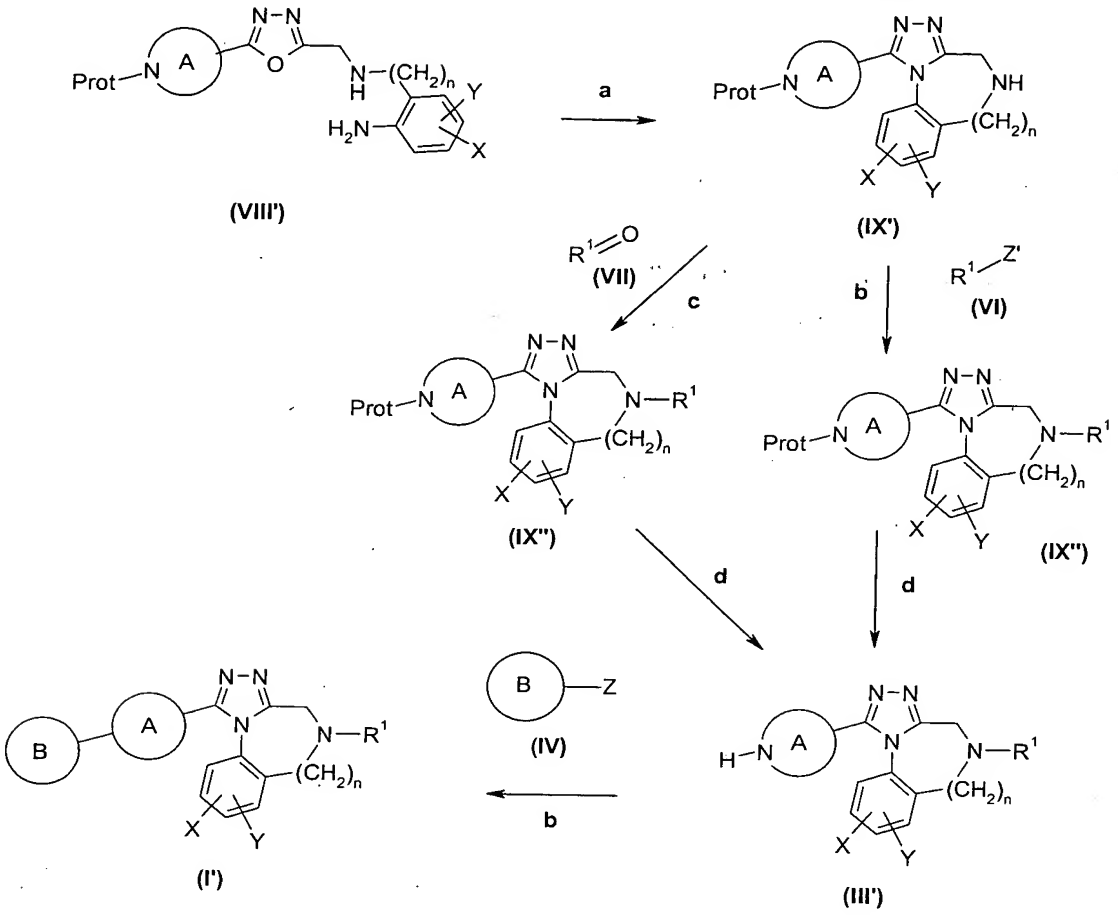
hydrogen chloride in a suitable solvent such as 1,4-dioxane at room temperature for 1-16 hours; or

a solution of trifluoroacetic acid in dichloromethane for 1-2 hours.

When Prot is CBz, the preferred method is hydrogenolysis using a suitable palladium catalyst in a solvent such as ethanol.

When Prot is an allyl carbamate, preferred conditions are thiobenzoic acid and a suitable palladium catalyst such as $Pd_2(Dba)_3$ with a suitable phosphine additive such as 1,4-bis(diphenylphosphino)butane in tetrahydrofuran for 20 minutes.

When ring B is linked to ring A via an N atom, and W represents NR^1 then:



Scheme 2.2

Prot represents a suitable protecting group for nitrogen, for example Boc, CBz or Allyl carbamate. Standard methodology for nitrogen protecting groups is used, such as that found in textbooks, (e.g. "Protecting Groups in Organic Synthesis" by T.W. Greene and P. Wutz).

Z represents halo (typically Cl). Z' represents a leaving group (typically Cl or OH).

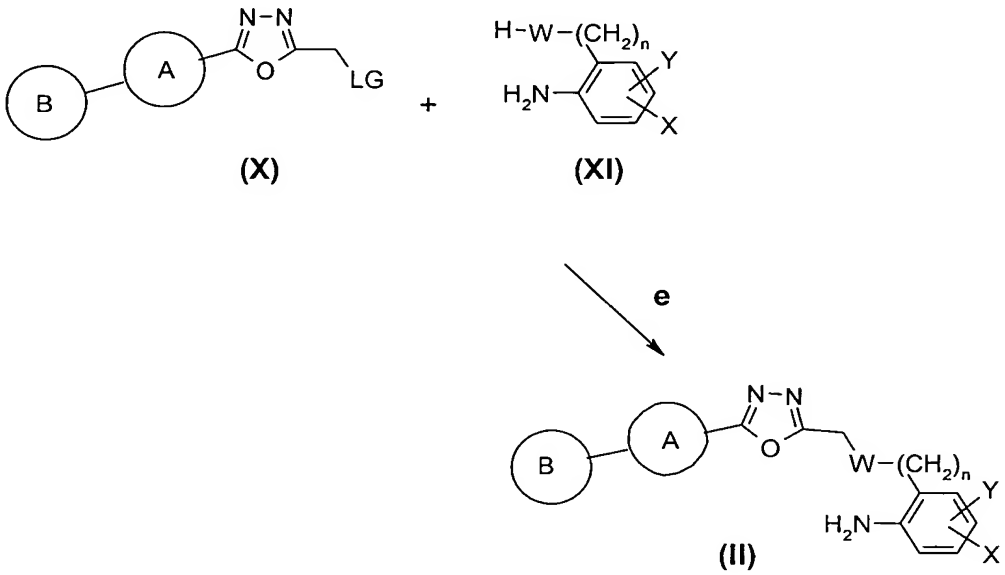
Compounds suitable for use as compound **(IV)** are commercially available or are known in the literature.

Compound **(IX")** typically can be prepared from compound **(IX')** using the methodology described in **Step (b)** and **Step (c)** above.

Compound **(III')** typically can be prepared from compound **(IX'')** using the methodology described in **Step (d)** above.

Compounds **(I')** typically can be prepared by arylation of compounds **(III')** using the methodology described in **Step (b)** above.

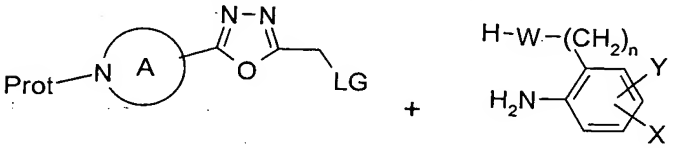
Compounds suitable for use as compounds **(II)** and **(VIII)** are known in the literature or can be prepared as shown in schemes 3.1 and 3.2 below.



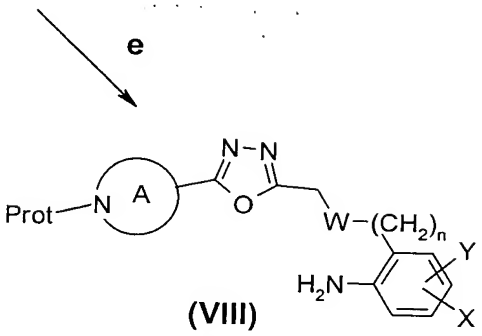
LG represents a leaving group, typically halo, and preferably chloro or bromo.

Scheme 3.1

When rings A and B are linked through an N atom then:



(XII) **(XI)**



(VIII)

LG is a leaving group, typically halo, and preferably chloro or bromo

Scheme 3.2

Compounds suitable for use as compounds **(XI)** are known in the literature or can be prepared using standard methodology: for example, reduction of benzoic acids (see preparation 7 below) or benzonitriles (see preparation 10 below).

When W represents NR^1:

Step (e): Compound **(X)/(XII)** is reacted with an excess of compound **(XI)** to give compound **(II)/(VIII)** respectively, optionally in the presence of an excess of base, such as triethylamine, Hünig's base or potassium carbonate as proton acceptor, in a suitable high boiling solvent such as THF, Toluene or DMF at temperatures from 50°C to 100°C for 1 to 48 hours.

Preferred conditions are:

2.5 eq. of compound **(XI)** in THF at 50°C for 48 hours.

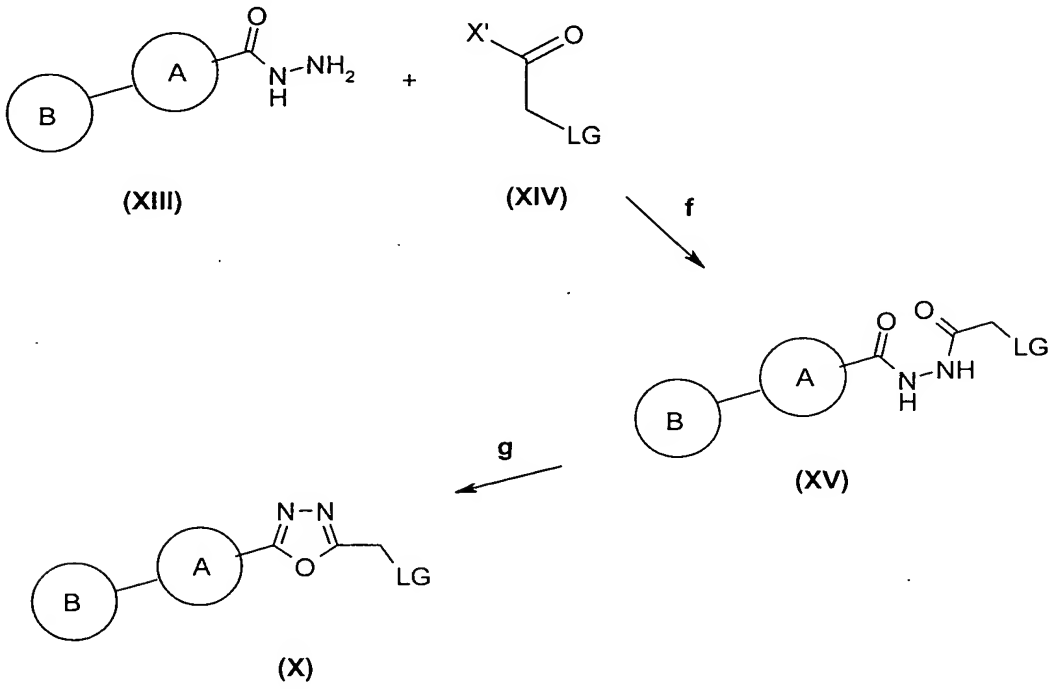
When W represents O or S:

Step (e): Compound **(X)/(XII)** is reacted with an excess of compound **(XI)** in the presence of a base such as sodium hydride, potassium hexamethyldisilazide, ^{n}butyl lithium or isopropyl magnesium chloride, in a suitable solvent such as THF, Toluene or NMP at temperatures from 0°C to 50°C for 1 to 24 hours, to give compound **(II)/(VIII)** respectively.

Preferred conditions are:

3 eq. of compound **(XI)** and 2.5 eq. of NaH in THF at 20°C for 2 hours.

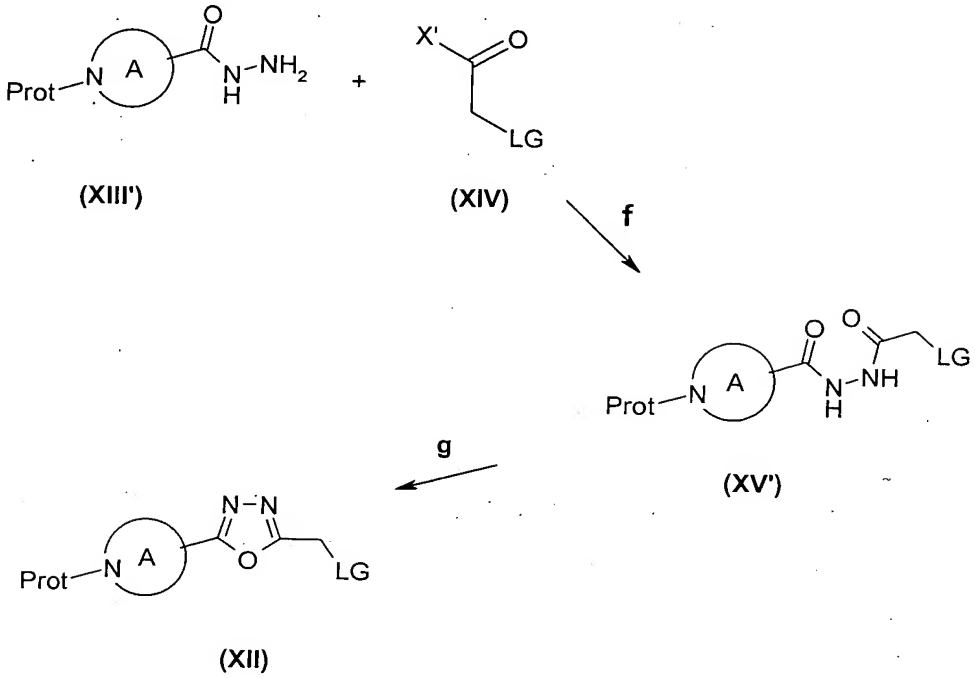
Compounds suitable for use as compounds **(X)** and **(XII)** are known in the literature or can be prepared as shown in scheme 4.1 and 4.2.



Scheme 4.1

X' represents OH or halo, and preferably represents Cl. LG represents a leaving group, typically halo, and preferably chloro or bromo

When rings A and B are linked through an N atom then:



(XIII') **(XIV)** **(XV')** **(XII)**

Scheme 4.2

X' represents OH or halo, and preferably represents Cl. LG is a leaving group, typically halo, and preferably chloro or bromo

Compound **(XIV)** is either commercially available or is known in the literature.

Step (f): The reaction of hydrazide **(XIII/XIII')** with compound **(XIV)** can be carried out by standard methods.

Coupling may be undertaken by using either:

(i) an acyl chloride **(XIV)** + hydrazide **(XIII/XIII')** with an excess of acid acceptor in a suitable solvent; or

(ii) acid **(XIV)** with a conventional coupling agent + hydrazide **(XIII/XIII')**, optionally in the presence of a catalyst, with an excess of acid acceptor in a suitable solvent.

Typically the conditions are as follows:

(i) acid chloride **(XIV)** (generated in-situ), an excess of hydrazide **(XIII/XIII')** , optionally with an excess of 3° amine such as Et_3N, Hünig's base or NMM, in DCM or THF, without heating for 1 to 24 hrs; or

(ii) acid **(XIV)**, WSCDI /DCC and HOBT /HOAT, an excess of hydrazide **(XIII/XIII')**, with an excess of NMM, Et_3N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 48 hrs; or

(ii) acid **(XIV)**, PYBOP®/PyBrOP®/Mukaiyama's reagent, an excess of hydrazide **(XIII/XIII')**, with an excess of NMM, Et_3N, Hünig's base in THF, DCM or EtOAc, at rt. for 4 to 24 hrs.

The preferred conditions are:

Hydrazide **(XIII/XIII')**, 1.5 eq. chloro acetyl chloride **(XIV)**, 1.5 eq. NMM in DCM at rt. for 16 hours.

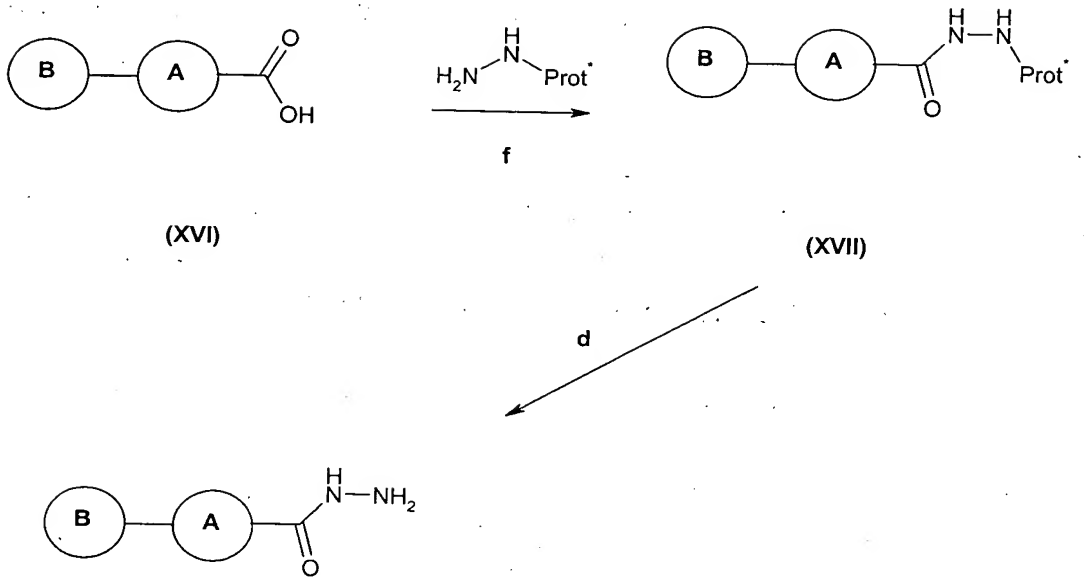
Step (g): Cyclisation of compound **(XV/XV')** is carried out under suitable dehydrating conditions, at elevated temperatures for up to 18 hours.

Typically, dehydrating agents such as polyphosphoric acid, phosphorous oxychloride, triflic anhydride are used at temperatures from 20 to 120°C for 5 minutes to 12 hours. Optionally, the reaction can be carried out in the presence of a base such as pyridine and suitable solvents such as dichloromethane and acetonitrile. Alternatively, the oxadiazole **(XII/X)** may be prepared according to the method of Rigo et. al. Synth. Commun. 16(13), 1665, 1986.

Preferred conditions are:

Phosphorous oxychloride at 100°C for 8 hours, or 2.5 eq. triflic anhydride, 5 eq. pyridine in dichloromethane at 20°C for 3 hours.

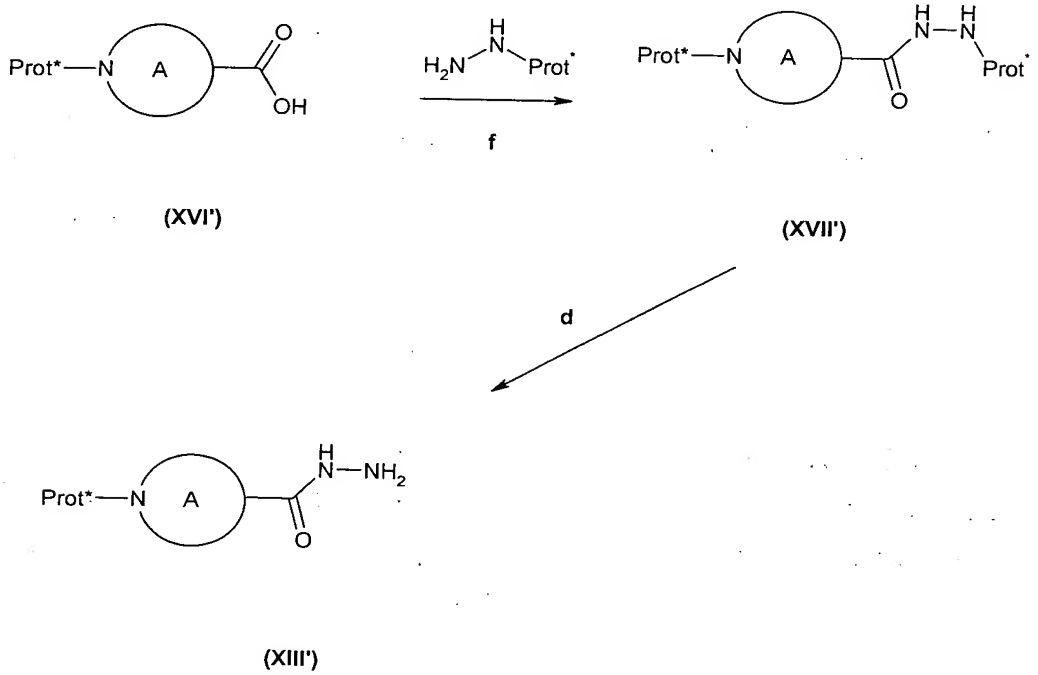
Compounds suitable for use as compounds **(XIII/XIII')** are known in the literature or can be prepared as shown in scheme 5.1 and 5.2.



(XIII)

Scheme 5.1

When rings A and B are linked through an N atom then:



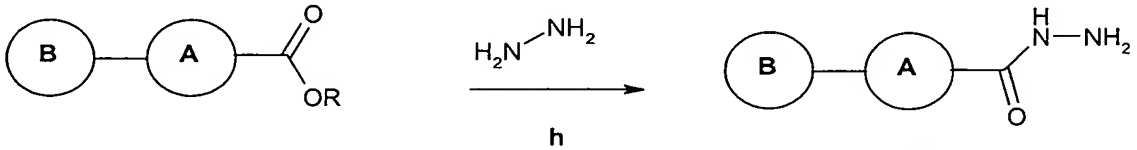
(XIII')

Scheme 5.2

Compounds **(XVI)/(XVI')** and protected hydrazine are either commercially available or are known in standard methodology such as the hydrolysis of the corresponding ester.

Carboxylic acid **(XVI)/(XVI')** and protected hydrazine, where prot* is typically Boc, may be coupled to give compound **(XVII/XVII')** respectively, using the conditions described above for the preparation of **(XV/XV')**, and then prot* is removed using standard methodology as described in **Step (d)** as described above, to give **(XIII/XIII')**.

Alternative routes to compound **(XIII/XIII')** are shown below in schemes 6.1 and 6.2:

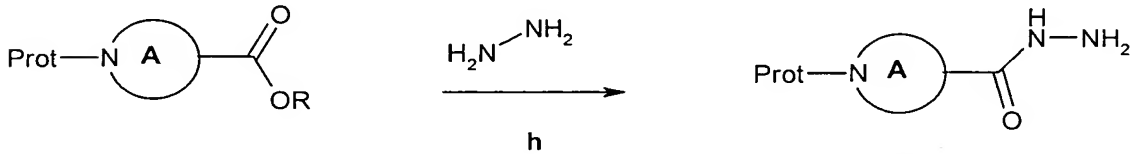


(XVIII) **(XIII)**

R is typically C_{1-2} alkyl

Scheme 6.1

When rings A and B are linked through an N atom then:



(XVIII') **(XIII')**

R is typically C_{1-2} alkyl

Scheme 6.2

Step (h): The ester **(XVIII/XVIII')** may be reacted with hydrazine in a suitable solvent, such as methanol, at an elevated temperature to provide the hydrazide **(XVII/XVII')**.

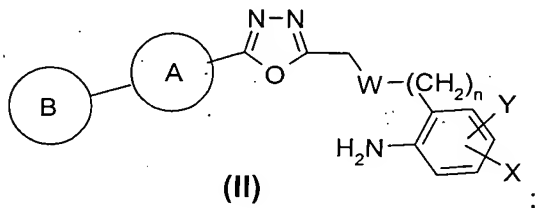
Preferred conditions:

3 eq. hydrazine, in methanol, at reflux for 18 hrs.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of formula **(I)**. This may be

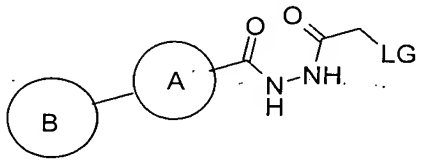
achieved by conventional techniques, for example as described in "Protective Groups in Organic Synthesis" by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991.

In accordance with the present invention there is further provided an intermediate of formula **(II)**:



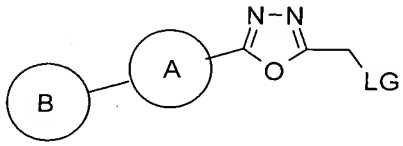
(II);

an intermediate of formula **(XV)**:



(XV)

an intermediate of formula **(X)**:



(X)

wherein X, Y, W, rings **A** and **B**, LG and n are as defined above.

The compounds of the present invention are useful because they possess pharmacological activity in animals. In particular they are useful in the treatment of a number of conditions including aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis. Particularly of interest is dysmenorrhoea.

Thus, according to another aspect of the invention, there is provided a method of treatment of dysmenorrhoea which comprises administering a therapeutically effective amount of a compound of the invention to a patient suffering from such a disorder. The use of the compounds as a medicament and the use of the compounds of the present invention in the manufacture of a medicament for the treatment of aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis, particularly dysmenorrhoea, are also provided.

The compounds of formula **(I)** may be freeze-dried, spray-dried or evaporatively dried to provide a solid plug, powder or film of crystalline or amorphous material. Microwave or radio frequency drying may be used for the purpose.

The compounds of the present invention may be administered alone or in combination with other drugs and will generally be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound of the invention. The choice of excipient will to a large extent depend on the particular mode of administration. Thus, according to another aspect of the present invention, there is provided a pharmaceutical formulation comprising a compound of formula (I) in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, films (including muco-adhesive), ovules and spray formulations

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example water, ethanol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

A typical tablet may be prepared using standard processes known to a formulation chemist, for example, by direct compression, granulation (dry, wet or melt), melt congealing or extrusion. The tablet formulation may comprise one or more layers and may be coated or uncoated.

Examples of excipients suitable for oral administration include carriers, for example, cellulose, calcium carbonate, dibasic calcium phosphate, mannitol and sodium citrate, granulation binders, for example, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose and gelatin, disintegrants, for example, sodium starch glycollate and silicates, lubricating agents, for example, magnesium stearate and stearic acid, wetting agents, for example, sodium lauryl sulphate, preservatives, anti-oxidants, flavours and colourants.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release. Details of suitable modified release technologies such as high energy dispersions, osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). Other modified release formulations are described in US Patent No. 6,106,864.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intreperitoneal, intrathecal, intraventricular, intraurethral, intranasal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous

solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula **(I)** used in the preparation of parenteral solutions may be increased by suitable processing, for example, the use of high energy spray-dried dispersions (see WO 01/47495) and/or by the use of appropriate formulation techniques, such as the use of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release.

The compounds of the invention may also be administered topically to the skin or mucosa, either dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petroleum, white petrolatum, glycerin and propylene glycol. Penetration enhancers may be incorporated - see, for example, J. Pharm. Sci., 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by iontophoresis, electroporation, phonophoresis, sonophoresis and needle-free or microneedle injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release. Thus compounds of the invention may be formulated in a more solid form for administration as an implanted depot providing long-term release of the active compound.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser with or without the use of a suitable propellant, such as dichlorofluoromethane.

The pressurised container, pump, spray, atomizer or nebuliser contains a solution or suspension of the active compound comprising, for example, ethanol (optionally, aqueous ethanol) or a suitable alternative agent for dispersing, solubilising or extending release of the active, the propellant(s) as solvent and an optional surfactant, such as sorbitans trioleate or an oligolactic acid.

Prior to use in a dry powder of suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such a spiral het milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation or spray drying.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 10mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100 µl. A typical formulation may comprise a compound of formula **(I)**, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Capsules, blisters and cartridges (made, for example, from gelatin of HPMC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol or magnesium stearate.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release.

The compounds of the invention may be combined with soluble macromolecular entities such as cyclodextrin or polyethylene glycol-containing polymers to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

For administration to human patients, the total daily dose of the compounds of the invention will typically be in the range of from about 0.01 to about 15 mg/kg of body weight, depending on the mode of administration. The total daily dose may be administered in a single dose or divided doses throughout the day.

The compounds of the present invention may be tested in the screens set out below:

1.0 V_{1A} Filter Binding Assay

1.1 Membrane Preparation

Receptor binding assays were performed on cellular membranes prepared from CHO cells stably expressing the human V_{1A} receptor, (CHO-hV_{1A}). The CHO-hV_{1A} cell line was kindly provided under a licensing agreement by Marc Thibonnier, Dept. of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio. CHO-hV_{1A} cells were routinely maintained at 37°C in humidified atmosphere with 5% CO_2 in DMEM/Hams F12

nutrient mix supplemented with 10 % fetal bovine serum, 2 mM L-glutamine, 15 mM HEPES and 400 µg/ml G418. For bulk production of cell pellets, adherent CHO-hV_{1A} cells were grown to confluency of 90-100% in 850 cm^2 roller bottles containing a medium of DMEM/Hams F12 Nutrient Mix supplemented with 10 % fetal bovine serum, 2 mM L-glutamine and 15 mM HEPES. Confluent CHO-hV_{1A} cells were washed with phosphate-buffered saline (PBS), harvested into ice cold PBS and centrifuged at 1,000 rpm. Cell pellets were stored at –80°C until use. Cell pellets were thawed on ice and homogenised in membrane preparation buffer consisting of 50 mM Tris-HCl, pH 7.4, 5 mM $MgCl_2$ and supplemented with a protease inhibitor cocktail, (Roche). The cell homogenate was centrifuged at 1000 rpm, 10 min, 4°C and the supernatant was removed and stored on ice. The remaining pellet was homogenised and centrifuged as before. The supernatants were pooled and centrifuged at 25,000 x g for 30 min at 4°C. The pellet was resuspended in freezing buffer consisting of 50 mM Tris-HCl, pH 7.4, 5 mM $MgCl_2$ and 20 % glycerol and stored in small aliquots at –80°C until use. Protein concentration was determined using Bradford reagent and BSA as a standard.

1.2 V_{1A} Filter binding

Protein linearity followed by saturation binding studies were performed on each new batch of membrane. Membrane concentration was chosen that gave specific binding on the linear portion of the curve. Saturation binding studies were then performed using various concentrations of [^{3}H]-arginine vasopressin, [^{3}H]-AVP (0.05 nM – 100 nM) and the K_d and B_{max} determined.

Compounds were tested for their effects on [^{3}H]-AVP binding to CHO-hV_{1A} membranes, (^{3}H-AVP; specific activity 65.5 Ci / mmol; NEN Life Sciences). Compounds were solubilised in dimethylsulfoxide (DMSO) and diluted to working concentration of 10% DMSO with assay buffer containing 50 mM Tris-HCL pH 7.4, 5 mM $MgCl_2$ and 0.05% BSA. 25 µl compound and 25 µl [^{3}H]-AVP, (final concentration at or below K_d determined for membrane batch, typically 0.5 nM – 0.6 nM) were added to a 96-well round bottom polypropylene plate. The binding reaction was initiated by the addition of 200 µl membrane and the plates were gently shaken for 60 min at room temperature. The reaction was terminated by rapid filtration using a Filtermate Cell Harvester (Packard Instruments) through a 96-well GF/B UniFilter Plate which had been presoaked in 0.5% polyethyleneimine to prevent peptide sticking. The filters were washed three times with 1 ml ice cold wash buffer containing 50 mM Tris-HCL pH 7.4 and 5 mM $MgCl_2$. The plates

were dried and 50 µl Microscint-0 (Packard instruments) was added to each well. The plates were sealed and counted on a TopCount Microplate Scintillation Counter (Packard Instruments). Non-specific binding (NSB) was determined using 1 µM unlabelled d(CH2)5Tyr(Me)AVP ([β-mercapto-β,β-cyclopentamethylenepropionyl,0-Me-Tyr^2,Arg^8]-vasopressin) (βMCPVP), (Sigma). The radioligand binding data was analysed using a four parameter logistic equation with the min forced to 0%. The slope was free fitted and fell between –0.75 and –1.25 for valid curves. Specific binding was calculated by subtracting the mean NSB cpm from the mean Total cpm. For test compounds the amount of ligand bound to the receptor was expressed as % bound = (sample cpm – mean NSB cpm)/specific binding cpm x100. The % bound was plotted against the concentration of test compound and a sigmoidal curve was fitted. The inhibitory dissociation constant (K_i) was calculated using the Cheng-Prusoff equation: $K_i=IC_{50}/(1+[L]/K_d)$ where [L] is the concentration of ligand present in the well and K_d is the dissociation constant of the radioligand obtained from Scatchard plot analysis.

2.0 V_{1A} Functional Assay; Inhibition of AVP / V_{1A}-R mediated Ca^{2+} mobilization by FLIPR (Fluorescent Imaging Plate Reader) (Molecular Devices)

Intracellular calcium release was measured in CHO-hV_{1A} cells using FLIPR, which allows the rapid detection of calcium following receptor activation. The CHO-hV_{1A} cell line was kindly provided under a licensing agreement by Marc Thibonnier, Dept. of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio. CHO-V_{1A} cells were routinely maintained at 37°C in humidified atmosphere with 5% CO_2 in DMEM/Hams F12 nutrient mix supplemented with 10 % fetal bovine serum, 2 mM L-glutamine, 15 mM HEPES and 400 µg/ml G418. On the afternoon before the assay cells were plated at a density of 20,000 cells per well into black sterile 96-well plates with clear bottoms to allow cell inspection and fluorescence measurements from the bottom of each well. Wash buffer containing Dulbecco's phosphate buffered saline (DPBS) and 2.5 mM probenecid and loading dye consisting of cell culture medium containing 4 µM Fluo-3-AM (dissolved in DMSO and pluronic acid),(Molecular Probes) and 2.5 mM probenecid was prepared fresh on the day of assay. Compounds were solubilised in DMSO and diluted in assay buffer consisting of DPBS containing 1% DMSO, 0.1% BSA and 2.5 mM probenecid. The cells were incubated with 100 µl loading dye per well for 1 hour at 37°C in humidified atmosphere with 5% CO_2. After dye loading the cells were washed three times in 100 µl wash buffer using a Denley plate washer. 100 µl wash buffer was left in each well.

Intracellular fluorescence was measured using FLIPR. Fluorescence readings were obtained at 2s intervals with 50 µl of the test compound added after 30s. An additional 155 measurements at 2s intervals were then taken to detect any compound agonistic activity. 50 µl of arginine vasopressin (AVP) was then added so that the final assay volume was 200 µl. Further fluorescence readings were collected at 1s intervals for 120s. Responses were measured as peak fluorescence intensity (FI). For pharmacological characterization a basal FI was subtracted from each fluorescence response. For AVP dose response curves, each response was expressed as a % of the response to the highest concentration of AVP in that row. For IC_{50} determinations , each response was expressed as a % of the response to AVP. IC50 values were converted to a modified K_b value using the Cheng-Prusoff equation which takes into account the agonist concentration, [A], the agonist EC_{50} and the slope: $K_b=IC_{50}/(2+[A]/A_{50}]^n)^{1/n}-1$ where [A] is the concentration of AVP, A_{50} is the EC_{50} of AVP from the dose response curve and n=slope of the AVP dose response curve.

The compounds of the invention have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stable, have fewer side effects or are more selective, or have other more useful properties than the compounds of the prior art.

Thus the invention provides:

(i) a compound of formula **(I)** or a pharmaceutically acceptable salt or solvate thereof;

(ii) a process for the preparation of a compound of formula **(I)** or a pharmaceutically acceptable salt or solvate thereof;

(iii) a pharmaceutical formulation including a compound of formula **(I)** or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipients, diluent or carrier;

(iv) a compound of formula **(I)** or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the use of a compound of formula **(I)** or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis,

cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis;

(vi) use as in (v) where the disease or disorder is dysmenorrhoea;

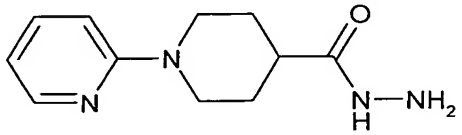
(vii) a method of treatment of a mammal to treat aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male and female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection, urolithiasis including treating said mammal with an effective amount of a compound of formula **(I)** or with a pharmaceutically acceptable salt, solvate or composition thereof;

(viii) a method as in (vii) where the disease or disorder is dysmenorrhoea;

(ix) intermediates of the formula **(II)**, **(XV)** and **(X)**;

The invention is illustrated by the following preparations and examples:

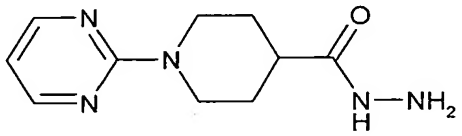
Preparation 1: 3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid hydrazide



3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid ethyl ester (1 g, 4.3 mmol)(see reference Farmaco, 1993, 48(10), 1439) was dissolved in methanol (20 ml) containing hydrazine hydrate (620 µl, 20 mmol) and was heated under reflux for 18 hours. The mixture was cooled to room temperature and evaporated under reduced pressure. The solid formed was triturated with propan-2-ol to give the title compound as a white solid (493 mg).

APCI MS *m/z* 221 $[M+H]^+$

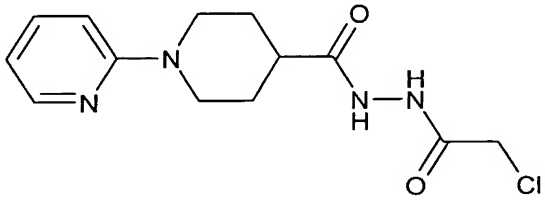
Preparation 2: 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid hydrazide



The title compound was obtained from 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid ethyl ester (see Farmaco, 1993, 48(10), 1439) in 91% yield following the procedure described in preparation 1.

APCI MS *m/z* 222 $[M+H]^+$

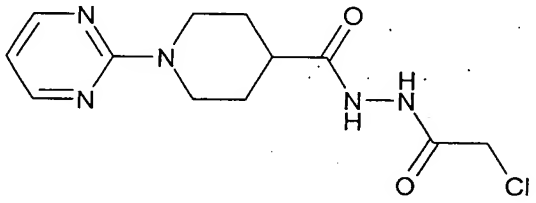
Preparation 3: 3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl-4-carboxylic acid N'-(2-chloro-acetyl)-hydrazide



The hydrazide of Preparation 1 (23.6 g, 0.11 mol) was suspended in dichloromethane (500 ml) and 4-methylmorpholine (17.7 ml, 0.16 mol) was added. The mixture was cooled using an ice bath and chloroacetyl chloride (12.8 ml, 0.16 mol) was added drop wise. The reaction was warmed to room temperature and was stirred for 3 hours. The solid formed

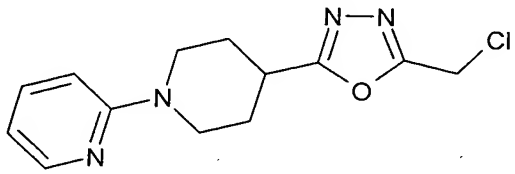
was isolated by filtration washed with dichloromethane and diethyl ether and dried under vacuum to give the title compound (20.4 g).
LCMS: *m/z* ES$^+$ 297 $[M+H]^+$

Preparation 4: 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid N'-(2-chloro-acetyl)-hydrazide



The title compound was prepared from the hydrazide of preparation 2 and chloroacetyl chloride, in 96% yield, using the procedure described in preparation 3.
APCI MS *m/z* 298 $[M+H]^+$

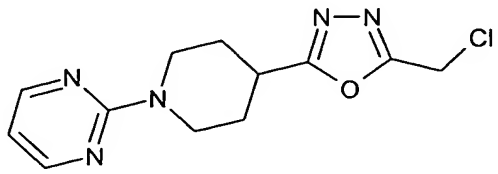
Preparation 5: 4-(5-Chloromethyl-[1,3,4]oxadiazol-2-yl)-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl



The hydrazide of Preparation 3 (20.4 g, 69 mmol) was suspended in phosphorus oxychloride (150 ml) at 100°C for 4 hours. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and was added to water. The aqueous layer was basified by addition of solid sodium hydrogen carbonate and the phases were separated. The aqueous phase was extracted with ethyl acetate (x2) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The material isolated was triturated with diethyl ether to give the title compound as a beige solid (15 g).

^{1}H NMR (400MHz, CD_3OD): δ 1.91 (m, 2H), 2.19 (m, 2H), 3.14 (m, 2H), 3.30 (m, 1H), 4.29 (m, 2H), 4.86 (s, 2H), 6.69 (m, 1H), 6.89 (d, 1H), 7.58 (m, 1H), 8.08 (d, 1H)

Preparation 6: 2-[4-(5-Chloromethyl-[1,3,4]oxadiazol-2-yl)-piperidin-1-yl]-pyrimidine

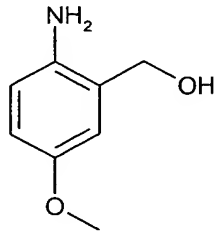


The title compound was prepared from the hydrazide of preparation 4, in 84% yield, using the procedure described in preparation 5.

APCI MS *m/z* 280 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.91 (m, 2H), 2.19 (m, 2H), 3.14 (m, 3H), 4.65 (s, 2H), 4.86 (m, 2H), 6.49 (m, 1H), 6.89 (d, 1H), 8.35 (d, 1H)

Preparation 7: (2-Amino-5-methoxy-phenyl)-methanol

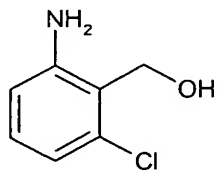


2-Amino-5-methoxy-benzoic acid (2.0 g, 12 mmol) in tetrahydrofuran (20 ml) was added drop wise to an ice cooled 1 molar solution of lithium aluminium hydride (14.4 ml) in tetrahydrofuran and stirred at 5°C for 2hr. Water (0.5 ml) was added drop wise followed by 2 molar aqueous sodium hydroxide solution (0.5 ml). The resulting emulsion was dried over magnesium sulphate, filtered and evaporated under reduced pressure to give the title compound as a yellow solid (766 mg).

APCI MS *m/z* 154 $[M+H]^+$

^1H NMR (400MHz, CD_3OD): δ 3.70 (s, 3H), 4.55 (s, 2H), 6.65-6.78 (m, 3H)

Preparation 8: (2-Amino-6-chloro-phenyl)-methanol

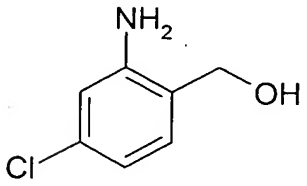


The title compound was prepared from 2-Amino-6-chloro-benzoic acid, in 69% yield as an off white solid, following the procedure described in preparation 7.

APCI MS *m/z* 158 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 4.85 (s, 2H), 6.60 (d, 1H), 6.80 (d, 1H), 7.00 (t, 1H)

Preparation 9: (2-Amino-4-chloro-phenyl)-methanol

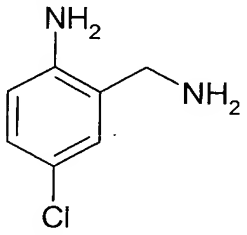


The title compound was prepared from 2-Amino-4-chloro-benzoic acid, in 48% yield as an off white solid, following the procedure described in preparation 7.

APCI MS *m/z* 170 $[MNa]^+$

^1H NMR (400MHz, CD_3OD): δ 4.55 (s, 2H), 6.60 (d, 1H), 6.70 (d, 1H), 7.00 (d, 1H)

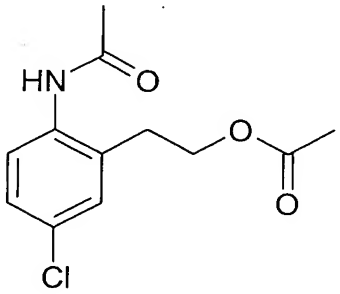
Preparation 10: 2-Aminomethyl-4-chloro-phenylamine



2-Amino-5-chloro-benzonitrile (9.0 g, 59 mmol) in tetrahydrofuran (100ml) was added drop wise to an ice cooled 1 molar solution of lithium aluminium hydride (100 ml) in tetrahydrofuran and stirred at room temperature for 18hr. Water (10 ml) was added drop wise. The resulting emulsion was dried over magnesium sulphate, filtered and evaporated under reduced pressure to give the title compound as a white solid (4.56 g).

^1H NMR (400MHz, $CDCl_3$): δ 3.85 (s, 2H), 4.50 (s, 2H), 6.60 (d, 1H), 7.05 (m, 2H)

Preparation 11: Acetic acid 2-(2-acetylamino-5-chloro-phenyl)-ethyl ester



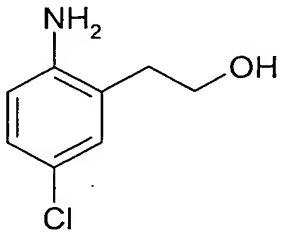
A solution of chlorine in glacial acetic acid (0.98M, 30 ml) was added drop wise to a solution of N-[2-(2-Hydroxy-ethyl)-phenyl]-acetamide (5.0 g, 27.9 mmol)(see reference Biochemistry 1979, 18(5), 860) in glacial acetic acid (50 ml) and stirred at room temperature for 20hr. Glacial acetic acid was removed under reduced pressure. The

resulting oil was triturated with diethyl ether to give the title compound (3.3 g) as a pale yellow solid after filtration.

APCI MS *m/z* 256, $[MH]^+$, 278 $[MNa]^+$

^1H NMR (400MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.26 (s, 3H), 2.87 (t, 2H), 4.13 (t, 2H), 7.11 (d, 1H), 7.23 (dd, 1H), 8.05 (d, 1H), 8.27 (s, 1H).

Preparation 12: 2-(2-Amino-5-chloro-phenyl)-ethanol

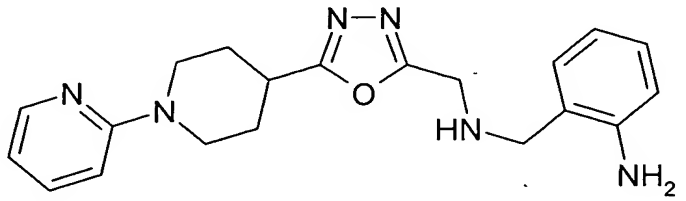


The compound from preparation 11 was suspended in 2 molar aqueous hydrochloric acid (20 ml) and heated to 100°C for 4hr. The solution was allowed to cool, made basic (pH 9) with 0.880 aqueous ammonia and partitioned with ethyl acetate (50 ml). The organic layer was washed with water, saturated brine and dried over magnesium sulphate. Filtration and evaporation under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane as eluant (5:0.5:95) to give the title compound as a brown oil (0.43 g).

APCI MS *m/z* 172, $[MH]^+$

^1H NMR (400MHz, CD_3OD): δ 2.64 (t, 2H), 3.69(t, 2H), 6.61 (d, 1H), 6.87 (dd, 1H), 6.93 (d, 1H).

Preparation 13: 2-({[5-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethyl]-amino}-methyl)-phenylamine



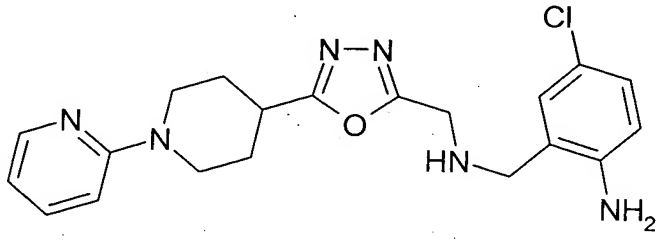
A solution of 2-Aminomethyl-phenylamine (2.2 g, 17.9 mmol) in tetrahydrofuran (50 ml) was added to a solution of the oxadiazole of preparation 5 (2.0 g, 7.18 mmol) in tetrahydrofuran (50 ml) and heated to 50°C for 18hr. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel using

methanol and ammonium hydroxide in dichloromethane as eluant (5:0.5:95) to give the title compound as a pale yellow gum (2.6 g).

APCI MS *m/z* 365 $[MH]^+$, 387 $[MNa]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.94 (m, 2H), 2.18(m, 2H), 3.14 (m, 3H), 3.88(s, 2H), 4.00 (s, 2H), 4.31 (m, 2H), 6.60-6.75 (m, 4H), 7.02 (d, 1H), 7.12 (t, 1H), 7.48 (t, 1H), 8.20 (d, 1H).

Preparation 14: 4-Chloro-2- ({[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethyl]-amino}-methyl)-phenylamine

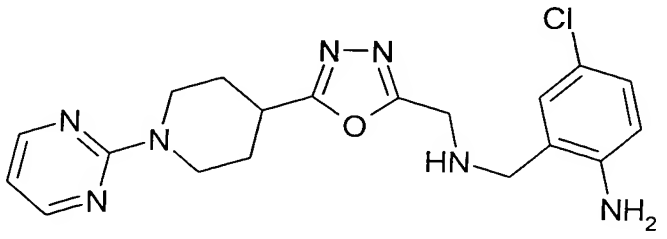


A solution of amine of preparation 10 (6.4 g, 41 mmol) in tetrahydrofuran (50 ml) was added to a solution of the oxadiazole of preparation 5 (4.56 g, 16 mmol) in tetrahydrofuran (50 ml) and heated to 50°C for 18hr. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel using methanol in dichloromethane as eluant (5:95) to give the title compound as a white solid (4.65 g).

APCI MS *m/z* 399 $[MH]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.95 (m, 2H), 2.20(m, 2H), 3.10 (m, 2H), 3.20 (m, 1H), 3.80(s, 2H), 4.00 (s, 2H), 4.30 (m, 2H), 6.60 (m, 1H), 6.65 (t, 1H), 6.70 (d, 1H), 7.00 (s, 1H), 7.05 (d, 1H), 7.50 (t, 1H), 8.20 (d, 1H)

Preparation 15: 4-Chloro-2-({[5-(1-pyrimidin-2-yl-piperidin-4-yl)-[1,3,4]oxadiazol-2-ylmethyl]-amino}-methyl)-phenylamine



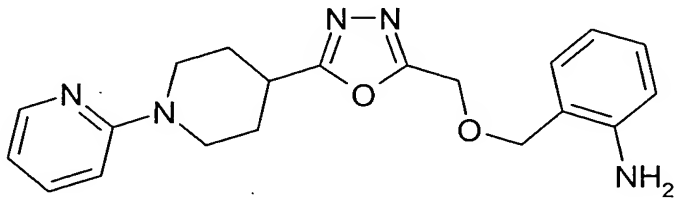
A solution of amine of preparation 10 (4.12 g, 26 mmol) in tetrahydrofuran (50 ml) was added to a solution of the oxadiazole of preparation 6 (2.95 g, 11 mmol) in

tetrahydrofuran (50 ml) and heated to 50°C for 18hr. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel using ethyl acetate as eluant to give the title compound as an off white solid (2.34 g).

APCI MS *m/z* 400 $[MH]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.80 (m, 2H), 2.20 (m, 2H), 3.20 (m, 3H), 3.80 (s, 2H), 4.00 (s, 2H), 4.75 (m, 2H), 6.50 (t, 1H), 6.60 (d, 1H), 7.00 (d, 1H), 7.05 (d, 1H), 8.35 (d, 2H).

Preparation 16: 2-[5-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

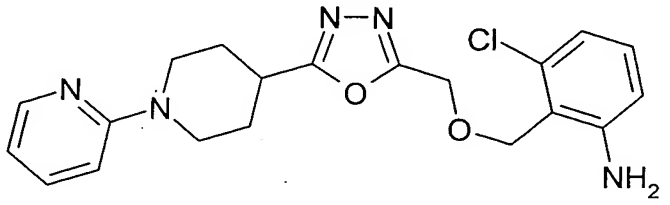


A solution of (2-Amino-phenyl)-methanol (996 mg, 8 mmol) in tetrahydrofuran (5ml) was added drop wise to an ice cooled suspension of sodium hydride (60% in mineral oil, 324 mg, 8.1 mmol) in tetrahydrofuran (5 ml) and stirred for 0.5hr. A solution of the oxadiazole of preparation 5 (750 mg, 2.69 mmol) in tetrahydrofuran (5 ml) was added drop wise and the mixture stirred at room temperature for 3hr. Ethyl acetate (50 ml) was added and the solution was extracted with water (25 ml). The aqueous solution was washed with ethyl acetate (2x20 ml) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using a gradient of ethyl acetate in pentane as eluant (2:1 to 100:0) to give the title compound (300 mg) as a white solid.

APCI MS *m/z* 366 $[MH]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.90 (m, 2H), 2.20 (m, 2H), 3.10 (m, 2H), 3.20 (m, 1H), 4.20 (s, 2H), 4.35 (m, 2H), 4.64 (s, 2H), 4.66 (s, 2H), 6.65 (m, 4H), 7.05 (d, 1H), 7.15 (t, 1H), 7.50 (t, 1H), 8.20 (d, 1H).

Preparation 17: 3-Chloro-2-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

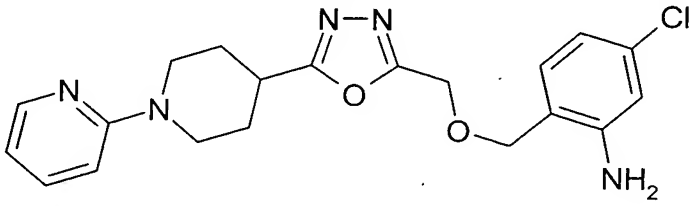


The title compound was prepared from the alcohol of preparation 8 and the oxadiazole of preparation 5, in 55% yield, using the procedure described in preparation 16.

APCI MS *m/z* 400 $[MH]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.95 (m, 2H), 2.20 (m, 2H), 3.05 (m, 2H), 3.20 (m, 1H), 4.30 (m, 2H), 4.40 (s, 2H), 4.70 (s, 2H), 4.90 (s, 2H), 6.55 (d, 1H), 6.60 (m, 1H), 6.70 (d, 1H), 6.75 (d, 1H), 7.00 (t, 1H), 7.15 (t, 1H), 7.45 (t, 1H), 8.20 (d, 1H).

Preparation 18: 5-Chloro-2-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

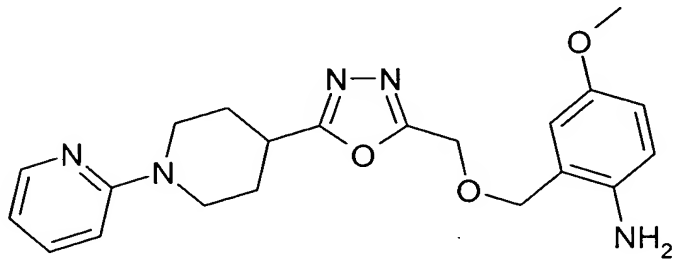


The title compound was prepared from the alcohol of preparation 9 and the oxadiazole of preparation 5, in 42% yield, using the procedure described in preparation 16.

APCI MS *m/z* 400 $[MH]^+$, 422 $[MNa]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.90 (m, 2H), 2.20 (m, 2H), 3.10 (m, 3H), 4.30 (m, 4H), 4.60 (s, 2H), 4.65 (s, 2H), 6.75 (m, 4H), 7.00 (d, 1H), 7.45 (t, 1H), 8.20 (d, 1H).

Preparation 19: 4-Methoxy-2-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

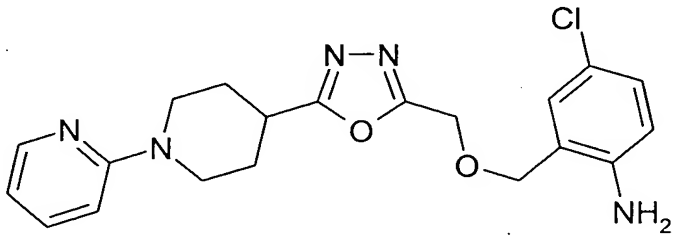


The title compound was prepared from the alcohol of preparation 7 and the oxadiazole of preparation 5, in 53% yield, using the procedure described in preparation 16.

APCI MS *m/z* 396 $[MH]^+$, 418 $[MNa]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.95 (m, 2H), 2.20 (m, 2H), 3.10 (m, 3H), 3.75 (s, 3H), 4.60 (s, 2H), 4.65 (s, 2H), 6.70 (m, 5H), 7.45 (t, 1H), 8.20 (d, 1H).

Preparation 20: 4-Chloro-2-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

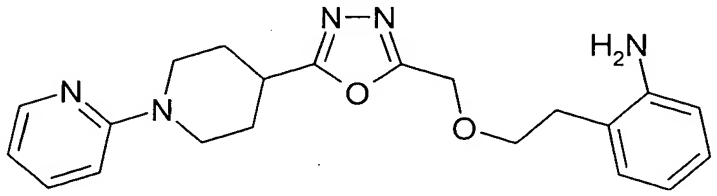


The title compound was prepared from (2-Amino-5-chloro-phenyl)-methanol and the oxadiazole of preparation 5, in 61% yield, using the procedure described in preparation 16.

APCI MS *m/z* 400 $[MH]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.95 (m, 2H), 2.20 (m, 2H), 3.10 (m, 2H), 3.20 (m, 1H), 4.20 (s, 2H), 4.35 (m, 2H), 4.60 (s, 2H), 4.70 (s, 2H), 6.60 (m, 2H), 6.70 (d, 1H), 7.10 (m, 2H), 7.45 (t, 1H), 8.20 (d, 1H).

Preparation 21: 2-{2-[5-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxy]-ethyl}-phenylamine

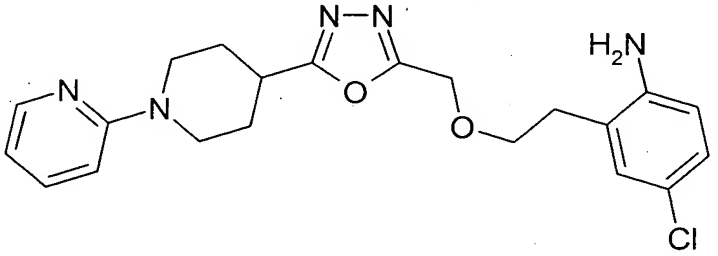


The title compound was prepared from 2-(2-Amino-phenyl)-ethanol and the oxadiazole of preparation 5, in 66% yield, using the procedure described in preparation 16.

APCI MS *m/z* 380 $[MH]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.95 (m, 2H), 2.15 (m, 2H), 2.80 (t, 2H), 3.10 (m, 3H), 3.80 (m, 4H), 4.30 (m, 2H), 4.65 (s, 2H), 6.70 (m, 4H), 7.00 (m, 2H), 7.50 (t, 1H), 8.20 (d, 1H).

Preparation 22: 4-Chloro-2-{2-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxy]-ethyl}-phenylamine

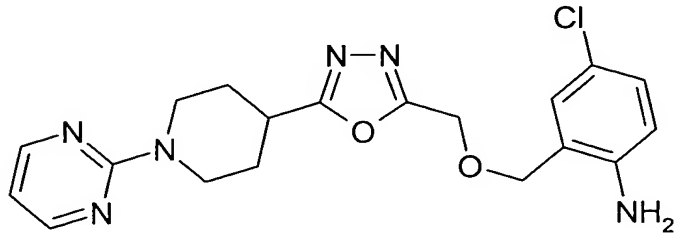


The title compound was prepared from the alcohol of preparation 12 and the oxadiazole of preparation 5, in 52% yield, using the procedure described in preparation 16.

APCI MS *m/z* 414 $[MH]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.92 (m, 2H), 2.15 (m, 2H), 2.77 (t, 2H), 3.10 (m, 3H), 3.79 (t, 2H), 4.28 (m, 2H), 4.66 (s, 2H), 6.58 (d, 1H), 6.62 (d, 1H), 6.71 (d, 1H), 6.97 (m, 2H), 7.49 (t, 1H), 8.20 (d, 1H).

Preparation 23: 4-Chloro-2-[5-(1-pyrimidin-2-yl-piperidin-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

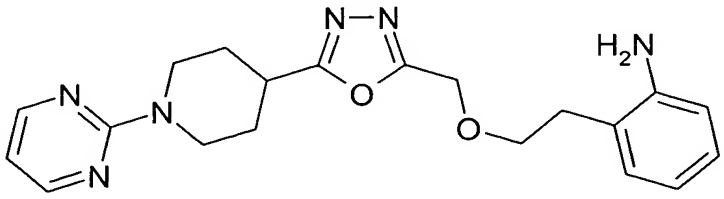


A solution of (2-Amino-5-chloro-phenyl)-methanol (850 mg, 5.4 mmol) in tetrahydrofuran (10 ml) was added drop wise to an ice cooled suspension of sodium hydride (60% in mineral oil, 215 mg, 5.4 mmol) in tetrahydrofuran (5 ml) and stirred for 1hr. A solution of the oxadiazole of preparation 6 (500 mg, 1.79 mmol) in tetrahydrofuran (5 ml) was added drop wise and the mixture stirred at room temperature for 1hr. Dichloromethane (50 ml) was added and the solution was extracted with water (25 ml). The aqueous solution was washed with dichloromethane (2x20 ml) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using diethyl ether followed by ethyl acetate as eluant to give, after trituration with diethyl ether, the title compound (320 mg) as a white solid.

APCI MS *m/z* 401 $[MH]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.92 (m, 2H), 2.19 (m, 2H), 3.24 (m, 3H), 4.60 (s, 2H), 4.68 (s, 2H), 4.75 (m, 2H), 6.57 (m, 1H), 6.63 (d, 1H), 7.08 (m, 2H), 8.37 (d, 2H).

Preparation 24: 2-{2-[5-(1-Pyrimidin-2-yl-piperidin-4-yl)-[1,3,4]oxadiazol-2-ylmethoxy]-ethyl}-phenylamine

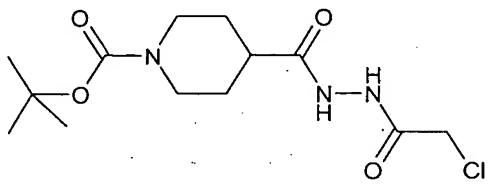


The title compound was prepared from 2-(2-Amino-phenyl)-ethanol and the oxadiazole of preparation 6, in 54% yield, using the procedure described in preparation 23.

APCI MS *m/z* 381 $[MH]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.85 (m, 2H), 2.15 (m, 2H), 2.88 (m, 2H), 3.18 (m, 3H), 1H), 3.80 (t, 2H), 4.68 (s, 2H), 4.74 (m, 2H), 6.51 (m, 1H), 6.80 (m, 2H), 7.08 (m, 2H), 8.37 (d, 2H).

Preparation 25: 4-[N'-(2-Chloro-acetyl)-hydrazinocarbonyl]-piperidine-1-carboxylic acid tert-butyl ester

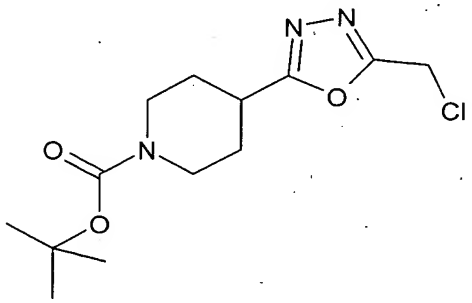


4-Hydrazinocarbonyl-piperidine-1-carboxylic acid tert-butyl ester (see reference WO 9703986 A1 19970206)(25 g, 103 mmol) was dissolved in dichloromethane (300 ml) and 4-methylmorpholine (12.5 ml, 113 mmol) was added. The mixture was cooled using an ice bath and chloroacetyl chloride (8.2 ml, 103 mmol) was added drop wise. The reaction was warmed to room temperature and was stirred for 4 hours. The reaction mixture was partitioned with aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and the filtrate evaporated to give the title compound as an off white solid (29.6 g).

APCI MS *m/z* 318 $[M-H]^+$

Found; C, 48.01; H, 6.91; N, 12.85; $C_{13}H_{22}N_3O_4Cl$ 0.3 H_2O requires; C, 48.02; H, 7.01; N, 12.92%.

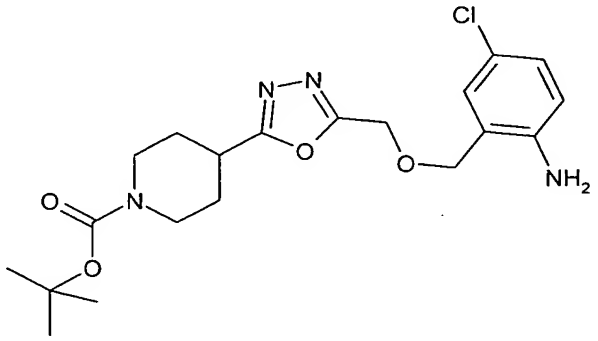
Preparation 26: 4-(5-Chloromethyl-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



The hydrazide of preparation 25 (5.0 g, 15.6 mmol) was suspended in dichloromethane (200 ml) and pyridine (6.4 ml, 78 mmol) added before cooling the mixture to 10°C. Trifluoroacetic anhydride (6.6 ml, 39 mmol) was added drop wise over 15 min and then stirred at room temperature for 3 hr. Reaction mixture partitioned with water (50ml), the organic layer was dried over magnesium sulphate, filtered and the filtrate evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (2:98) to give the title compound as a white solid (2.95 g).

^{1}H NMR (400MHz, CD_3OD): δ 1.45 (s, 9H), 1.74 (m, 2H), 2.19 (m, 2H), 3.04 (m, 2H), 3.24 (m, 1H), 4.09 (m, 2H), 4.85 (s, 2H)

Preparation 27: 4-[5-(2-Amino-5-chloro-benzyloxymethyl)-[1,3,4]oxadiazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester

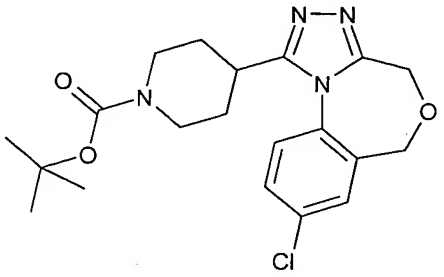


A solution of (2-Amino-5-chloro-phenyl)-methanol (1 g, 6.4 mmol) in tetrahydrofuran (10 ml) was added drop wise to an ice cooled suspension of sodium hydride (60% in mineral oil, 215 mg, 5.4 mmol) in tetrahydrofuran (5 ml) and stirred for 1hr. A solution of the oxadiazole of preparation 26 (1 g, 5.3 mmol) in tetrahydrofuran (5 ml) was added drop wise and the mixture stirred at room temperature for 2hr. The reaction mixture was partitioned between dichloromethane (50 ml) and sodium hydrogen carbonate solution (25 ml). The aqueous solution was washed with dichloromethane (2x20 ml) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol in dichloromethane (5:95) as eluant to give the title compound (1.3 g) as a yellow solid.

APCI MS *m/z* 423 $[MH]^+$, 323 $[M\text{-}Boc]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.81 (m, 2H), 2.07 (m, 2H), 2.96 (m, 2H), 3.08 (m, 1H), 4.12 (m, 2H), 4.23 (s, 2H), 4.58 (s, 2H), 4.68 (s, 2H), 6.62 (d, 1H), 7.07 (s, 1H), 7.12 (d, 1H).

Preparation 28: 4-(8-Chloro-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulen-1-yl)-piperidine-1-carboxylic acid tert-butyl ester



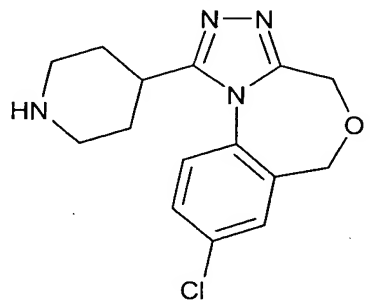
Toluene-4-sulfonic acid (80 mg, 0.46 mmol) was added to a solution of the oxadiazole of preparation 27 (1.28 g, 3.0 mmol) and heated to 140°C for 18hr. Xylene was removed under reduced pressure. The residue was partitioned between dichloromethane (100 ml) and sodium hydrogen carbonate solution (25 ml). The aqueous solution was washed with dichloromethane (2x20 ml) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound (730 mg) as a pale yellow foam.

APCI MS *m/z* 405 $[MH]^+$, 305 $[M\text{-}Boc]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.85 (m, 2H), 1.96 (m, 2H), 2.92 (m, 2H), 3.08 (m, 1H), 4.18 (m, 2H), 4.40 (s, 2H), 4.66 (s, 2H), 7.36 (d, 1H), 7.58 (m, 2H).

Found; C, 57.98; H, 6.17; N, 13.40; $C_{20}H_{25}N_4O_3Cl$ $0.5H_2O$ requires; C, 58.04; H, 6.33; N, 13.54%.

Preparation 29: 8-Chloro-1-piperidin-4-yl-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene



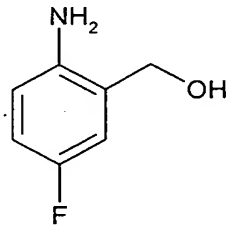
The triazole of preparation 28 (700 mg, 1.73 mmol) was dissolved in 1,4-dioxan (6 ml) and hydrochloric acid (4M in 1,4-dioxane, 12 ml) added. Reaction mixture stirred at room temperature for 4hr. 1,4-dioxane was removed under reduced pressure. The residue was partitioned between dichloromethane (100 ml) and sodium hydrogen carbonate solution

(25 ml). The aqueous solution was washed with dichloromethane (2x20 ml) and the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure to give the title compound (410 mg) as a pale yellow foam.

APCI MS *m/z* 305 $[MH]^+$

^{1}H NMR (400MHz, CD_3OD): δ 1.83 (m, 4H), 2.65 (t, 2H), 3.09 (m, 2H), 3.24 (m, 1H), 4.41 (s, 2H), 4.58 (s, 2H), 7.58 (m, 3H).

Preparation 30: (2-Amino-5-fluoro-phenyl)-methanol

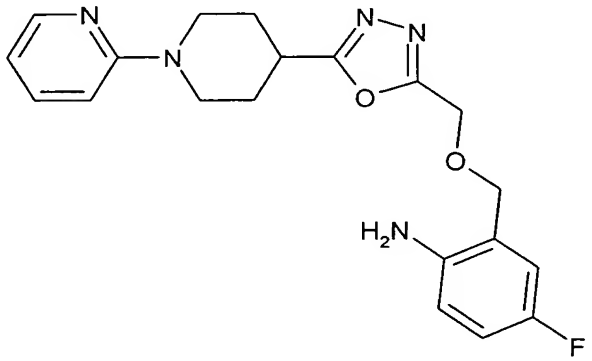


The title compound was prepared from 2-Amino-5-fluoro-benzoic acid, in 81% yield as an off white solid, following the procedure described in preparation 7.

APCI MS *m/z* 142 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 4.60 (s, 2H), 6.60 (dd, 1H), 6.77-6.86 (m, 2H)

Preparation 31: 4-Fluoro-2-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

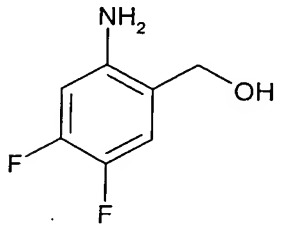


The title compound was prepared from the alcohol of preparation 30 and the oxadiazole of preparation 5, in 60% yield, using the procedure described in preparation 16.

APCI MS *m/z* 384 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.95 (dq, 2H), 2.18 (d, 2H), 3.06-3.21 (m, 3H), 4.33 (td, 2H), 4.60 (s, 2H), 4.70 (s, 2H), 6.58-.6.67 (m, 2H), 6.73 (d, 1H), 6.80-6.90 (m, 2H), 7.52 (t, 1H), 8.19 (d, 1H).

Preparation 32: (2-Amino-4,5-difluoro-phenyl)-methanol

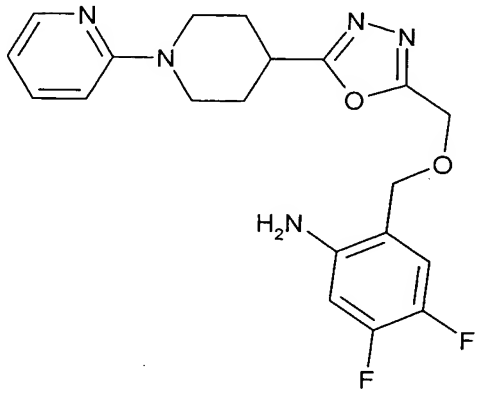


The title compound was prepared from 2-Amino-4, 5-difluoro-benzoic acid, in 86% yield as a yellow solid, following the procedure described in preparation 7.

APCI MS *m/z* 142 $[M+H-H_2O]^+$, 160 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 4.10 (bs, 2H), 4.58 (s, 2H), 6.48 (dd, 1H), 6.92 (dd, 1H)

Preparation 33: 4,5-difluoro-2-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

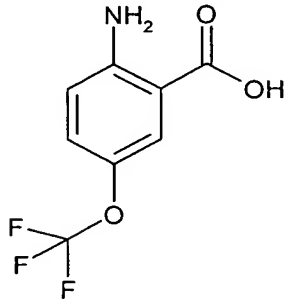


The title compound was prepared from the alcohol of preparation 32 and the oxadiazole of preparation 5, in 50% yield, using the procedure described in preparation 16.

APCI MS *m/z* 402 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.94 (dq, 2H), 2.09 (bd, 1H), 3.09 (bt, 2H), 3.18 (m, 1H), 4.20 (bs, 2H), 4.33 (td ,2H), 4.54 (s, 2H), 4.68 (s, 2H), 6.47 (dd, 1H), 6.64 (t, 1H), 6.72 (d, 1H)6.92 (dd, 1H), 7.52 (t, 1H), 8.19, (d, 1H)

Preparation 34: 2-Amino-5-trifluoromethoxy-benzoic acid

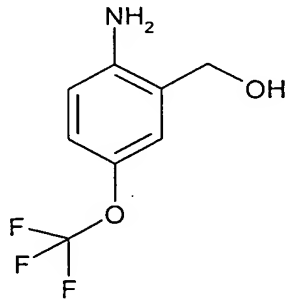


5-Trifluoromethoxy-1H-indole-2,3-dione (3.48g, 15.0 mmol) was dissolved in 2N aqueous sodium hydroxide (90ml) and cooled to 17°C before adding 30% aqueous hydrogen peroxide solution (2.75ml, 27 mmol) drop wise over 20 minutes. Mixture stirred at room temperature for 1hr before adding conc. Hydrochloric acid (7ml). The resulting brown precipitate was filtered off and dried *in vacuo* at 50°C for 66hrs to give the title compound (1.83g) as a brown solid.

APCI MS *m/z* 220 $[M-H]^+$

^{1}H NMR (400MHz, DMSO): δ 6.80 (d, 1H) 7.24 (dd, 1H), 7.53 (d, 1H)

Preparation 35: (2-Amino-5-trifluoromethoxy-phenyl)-methanol

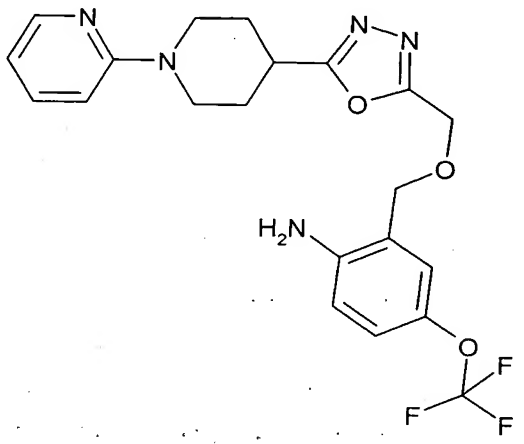


The title compound was prepared from the acid of preparation 34, in 62% yield as a white solid, following the procedure described in preparation 7.

APCI MS *m/z* 206 $[M-H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 4.85 (s, 2H), 6.67 (d, 1H), 6.92-7.00 (m, 2H)

Preparation 36: 2-[5-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-4-trifluoromethoxy-phenylamine

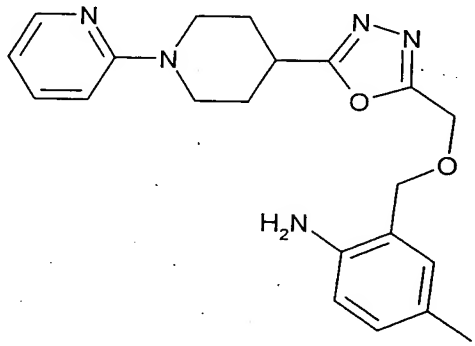


The title compound was prepared from the alcohol of preparation 35 and the oxadiazole of preparation 5, in 28% yield, using the procedure described in preparation 16.

APCI MS *m/z* 450 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.94 (dq, 2H), 2.16 (bd, 1H), 3.09 (t, 2H), 3.17 (m, 1H), 4.37 (bd, 2H), 4.60 (s ,2H), 4.67 (s, 2H), 6.60-6.66 (m, 2H), 6.70 (d, 1H), 6.95-7.07 (m, 2H), 7.49 (t, 1H) 8.19, (d, 1H)

Preparation 37: 4-Methyl-2-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethoxymethyl]-phenylamine

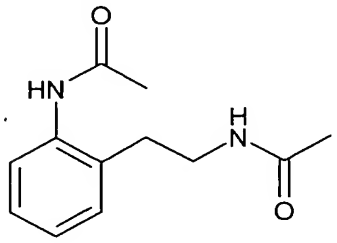


The title compound was prepared from (2-Amino-5-methyl-phenyl)-methanol (see Arch. Pharm. (1929), 583) and the oxadiazole of preparation 5, in 38% yield, using the procedure described in preparation 16.

APCI MS *m/z* 380 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.92 (dq, 2H), 2.16 (bd, 2H), 2.19 (s, 3H), 3.09 (t, 2H), 3.17 (m, 1H), 4.37 (bd, 2H), 4.60 (s, 2H), 4.67 (s, 2H), 6.64 (m, 2H), 6.85 (m, 3H), 7.58 (t, 1H) 8.09, (d, 1H)

Preparation 38: N-[2-(2-Acetylamino-ethyl)-phenyl]-acetamide



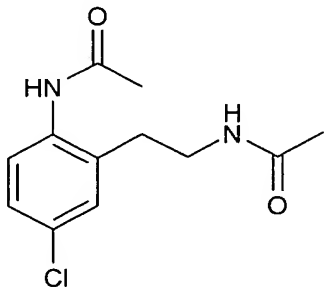
A solution of acetic anhydride (9.6 ml, 101 mmol) in dichloromethane (50 ml) was added drop wise to a solution of 2-(2-Amino-ethyl)-phenylamine (see JACS 99, (1977), 5716)(8.0 g, 46 mmol) and triethylamine (8.4 ml, 60 mmol) in dichloromethane (200 ml). Mixture was stirred at room temperature for 18 hr before partitioning with water (100 ml). The organic layer was washed with a saturated solution of brine (50 ml), dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound (4.1 g) as an off white solid.

APCI MS *m/z* 221 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.33 (s, 3H), 2.81 (t, 2H), 3.28 (m, 2H), 6.19 (bs, 1H), 7.03 (bt, 1H), 7.07 (d, 1H), 7.22 (m, 1H), 8.11 (d, 1H), 8.88 (bs, 1H)

Found C, 65.18%, H, 7.27%, N, 12.70%; $C_{12}H_{16}N_2O_2$ requires C, 65.43%, H, 7.32%. N, 12.72%

Preparation 39: N-[2-(2-Acetylamino-ethyl)-4-chloro-phenyl]-acetamide

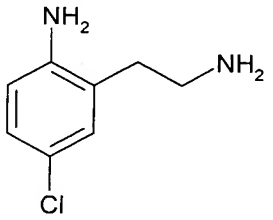


A solution of chlorine in glacial acetic acid (1.22M, 29 ml) was added drop wise to a solution of the acetamide of preparation 38 (7.78 g, 35 mmol) in glacial acetic acid (70 ml) and stirred at room temperature for 2hr. Glacial acetic acid was removed under reduced pressure. The resulting solid was triturated with a mixture of ethyl acetate and propan-2-ol (7:3, 20ml) to give the title compound (4.83 g) as a pale yellow solid after filtration.

ESI MS *m/z* 277 $[M+Na]^+$

^{1}H NMR (400MHz; $CDCl_3$): δ 2.03 (s, 3H), 2.33 (s, 3H), 2.79 (m, 2H), 3.22 (m, 2H), 6.28 (bs, 1H), 7.05 (s, 1H), 7.20 (dd, 1H), 8.14 (d, 1H), 9.09 (bs, 1H)

Preparation 40: 2-(2-Amino-ethyl)-4-chloro-phenylamine dihydrochloride



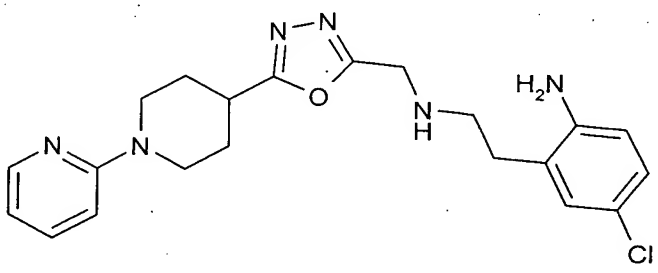
The compound from preparation 39 (4.83 g, 19 mmol) was suspended in 2 molar aqueous hydrochloric acid (50 ml) and heated to 100°C for 18hr. Evaporation under reduced pressure gave a red solid which was triturated with propan-2-ol (15ml) to give the title compound as a pale pink solid (3.5 g) after filtration.

ESI MS *m/z* 171 $[M+H]^+$

^{1}H NMR (400MHz, DMSO-d_6): δ 3.00 (t, 2H), 3.12 (m, 2H), 7.38 (dd, 1H), 7.40 (d, 1H), 7.46 (d, 1H), 8.15 (bs, 3H)

Found C, 39.29%, H, 5.45%, N, 11.46%; $C_8H_{11}N_2.2HCl$ requires C, 39.45%, H, 5.38%, N, 11.50%

Preparation 41: 4-Chloro-2-(2-{[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3,4]oxadiazol-2-ylmethyl]-amino}-ethyl)-phenylamine

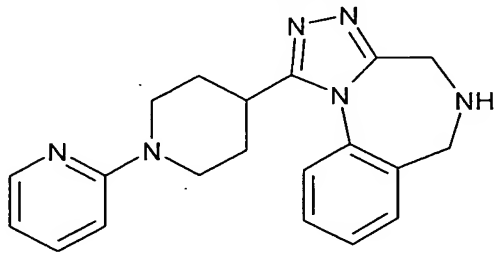


A solution of amine of preparation 40 (3.5 g, 14.4 mmol) in tetrahydrofuran (50 ml) was added to a solution of the oxadiazole of preparation 5 (4.0 g, 14.4 mmol) and triethylamine (7.0 ml, 50 mmol) in tetrahydrofuran (50 ml) and heated to 50°C for 4hr. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel using ethyl acetate as eluant followed by methanol and ammonium hydroxide in dichloromethane (5:0.5:95) to give the title compound as a brown oil (1.35 g).

APCI MS *m/z* 413 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.92 (dq, 2H), 2.15 (bdd, 2H), 2.68 (t, 2H), 2.93 (t, 2H), 3.07 (dt, 2H), 3.14 (m, 1H), 4.01 (s, 2H), 4.31 (btd, 2H), 6.57 (d, 1H), 6.62 (dd, 1H), 6.70 (d, 1H), 6.95-7.02 (m, 2H), 7.27 (t, 1H), 8.19 (d, 1H)

Example 1: 1-(3,4,5,6-Tetrahydro-2H- [1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

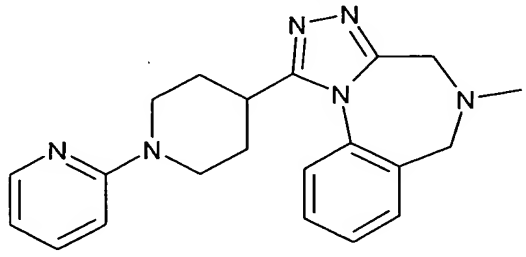


Toluene-4-sulfonic acid (100 mg, 0.58 mmol) was added to a solution of the oxadiazole of preparation 13 (2.45 g, 6.8 mmol) and heated to 150°C for 18hr. Mixture cooled and purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant followed by chromatography on silica gel using methanol and ammonium hydroxide in ethyl acetate (10:1:90) followed by methanol and ammonium hydroxide in dichloromethane (7:1:93) as eluant to give, after trituration with ethyl acetate, the title compound (770 mg) as a brown solid.

APCI MS *m/z* 347 $[MH]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.80-2.40 (m, 4H), 2.95 (m, 2H), 3.20 (m, 1H), 3.73 (s, 2H), 3.88 (s, 2H), 4.33 (m, 2H), 6.57 (m, 1H), 6.68 (d, 1H), 7.37 (d, 1H), 7.50 (m, 4H), 8.17 (d, 1H)

Example 2: 5-Methyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene



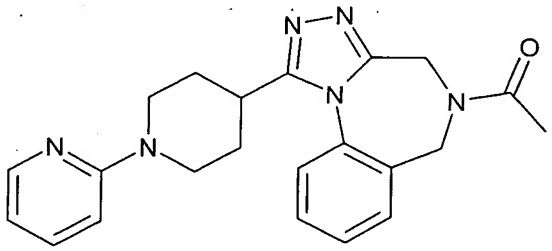
Formaldehyde (37% w/v aqueous, 1 ml, 81 mmol) was added to a solution of the amine of example 1 (100 mg, 0.28 mmol) in dichloromethane (20ml). Mixture stirred at room temperature for 0.25hr before adding sodium triacetoxyborohydride (500mg, 2.4 mmol)

and stirred for a further 0.25hr. Dichloromethane was removed under reduced pressure. Residue was partitioned between 2N aqueous sodium hydroxide solution (50ml) and ethyl acetate (50ml). The organic layer was washed with saturated brine and dried over magnesium sulphate before filtering and evaporating the filtrate under reduced pressure to give the title compound as a pale yellow foam (75 mg)

APCI MS *m/z* 361 $[MH]^+$, 384 $[MNa]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 2.08 (m, 4H), 2.52 (s, 3H), 3.00 (m, 2H), 3.21 (m, 2H), 3.40 (s, 2H), 3.70 (s, 2H), 4.36 (m, 2H), 6.60 (m, 1H), 6.68 (d, 1H), 7.40 (d, 1H), 7.50 (m, 4H), 8.18 (d, 1H)

Example 3: 1-[1-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-ethanone

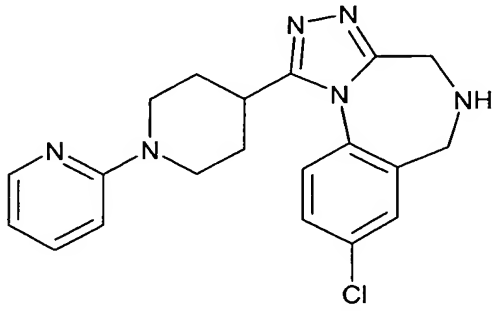


Acetyl chloride (22 mg, 0.29 mmol) was added to an ice cooled solution of the amine of example 1 (100 mg, 0.29 mmol) in dichloromethane (50ml) and stirred at room temperature for 2hr. Dichloromethane was evaporated off under reduced pressure and the residue purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound as a brown foam (102 mg).

APCI MS *m/z* 389 $[MH]^+$, 412 $[MNa]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.50 - 2.28 (m, 7H, rotamers), 3.01 (brs, 2H), 3.10 (m, 1H), 4.00 – 5.00 (m, 6H, rotamers), 6.61 (m, 1H), 6.68 (m, 1H), 7.50 (m, 3H), 7.61 (m, 2H), 8.18 (m, 1H)

Example 4: 8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene



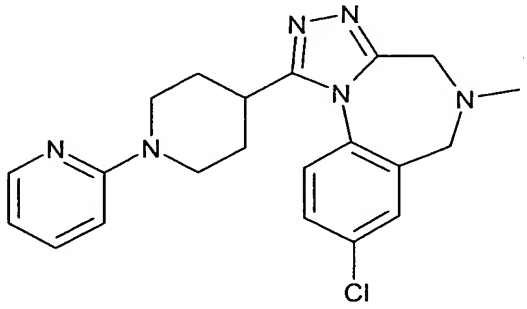
Toluene-4-sulfonic acid (100 mg, 0.58 mmol) was added to a solution of the oxadiazole of preparation 14 (4.65 g, 12 mmol) and heated to 140°C for 18hr. Mixture cooled and purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound (2.0 g) as an off white solid.

APCI MS *m/z* 381 $[MH]^+$, 403 $[MNa]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.80-2.20 (m, 4H), 2.95 (m, 2H), 3.14 (m, 1H), 3.68 (s, 2H), 3.92 (s, 2H), 4.36 (m, 2H), 6.60 (m, 1H), 6.67 (d, 1H), 7.35 (d, 1H), 7.50 (m, 3H), 8.17 (d, 1H)

Found; C, 59.90; H, 5.48; N, 20.50; $C_{20}H_{21}N_6Cl$ $0.33CH_2Cl_2$ requires; C, 59.72; H, 5.34; N, 20.55%.

Example 5: 8-Chloro-5-methyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene trihydrochloride



Formaldehyde (37% w/v aqueous, 0.1 ml, 1.2 mmol) was added to a solution of the amine of example 4 (200 mg, 0.53 mmol) in dichloromethane (5ml). Mixture stirred at room temperature for 0.25hr before adding sodium triacetoxyborohydride (500mg, 2.4 mmol) and stirred for a further 18hr. Reaction mixture was partitioned between 2N aqueous sodium hydroxide solution (10ml) and dichloromethane (10ml). The organic layer was

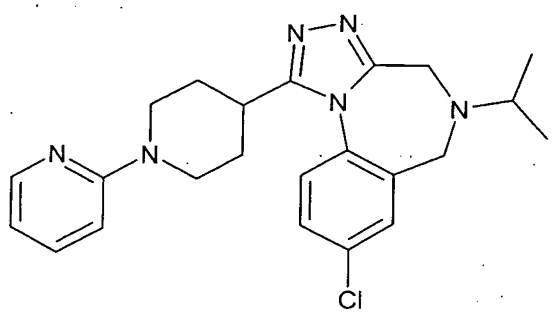
evaporated under reduced pressure and purified by chromatography on silica gel using methanol in dichloromethane (5:95) as eluant. The residue was dissolved in dichloromethane (2ml) and hydrochloric acid (1M in diethyl ether, 2ml) added and solvents evaporated under reduced pressure to give the title compound as a brown foam (96 mg).

APCI MS *m/z* 395 $[MH]^+$, 417 $[MNa]^+$

^{1}H NMR (400MHz, CD_3OD): δ 2.00 (m, 2H), 2.27 (m, 1H), 2.58 (m, 1H), 3.11 (s, 3H), 3.36 (m, 1H), 3.62 (m, 2H), 4.21 (m, 4H), 4.40 (m, 1H), 4.55 (m, 1H), 7.00 (t, 1H), 7.44 (d, 1H), 7.88 (m, 2H), 7.92 (m, 2H), 8.06 (t, 1H)

Found; C, 44.30; H, 5.52; N, 14.65; $C_{21}H_{23}N_6Cl$ $0.33CH_2Cl_2$. 3HCl. $2.5H_2O$ requires; C, 44.37; H, 5.53; N, 14.53%.

Example 6: 8-Chloro-5-isopropyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene trihydrochloride



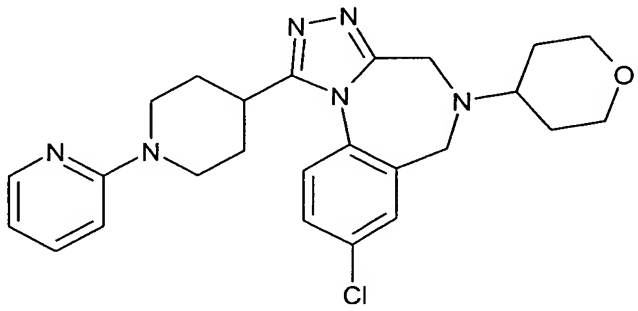
Acetone (0.1 ml, 1.36 mmol) was added to a solution of the amine of example 4 (200 mg, 0.53 mmol) in dichloromethane (5ml). Mixture stirred at room temperature for 0.25hr before adding sodium triacetoxyborohydride (500mg, 2.4 mmol) and stirred for a further 18hr. Reaction mixture was partitioned between 2N aqueous sodium hydroxide solution (10ml) and dichloromethane (10ml). The organic layer was evaporated under reduced pressure and purified by chromatography on silica gel using methanol in dichloromethane (5:95) as eluant. The residue was dissolved in dichloromethane (2ml) and hydrochloric acid (1M in diethyl ether, 2ml) added and solvents evaporated under reduced pressure to give the title compound as a brown foam (161 mg).

APCI MS *m/z* 423 $[MH]^+$, 445 $[MNa]^+$

^{1}H NMR (400MHz, CD_3OD): δ 1.57 (m, 6H), 2.00 (m, 2H), 2.24 (m, 1H), 2.58 (m, 1H), 3.38 (m, 1H), 3.58 (m, 1H), 3.70 (m, 1H), 3.86 (m, 1H), 4.23 (m, 3H), 4.40 (m, 1H), 4.62 (m, 1H), 5.00 (m, 1H), 7.00 (m, 1H), 7.43 (m, 1H), 7.80-8.06 (m, 5H)

Found; C, 46.51; H, 5.98; N, 13.96; $C_{23}H_{27}N_6Cl$ $0.28CH_2Cl_2$. 3HCl. $2.5H_2O$ requires; C, 46.51; H, 5.96; N, 13.98%.

Example 7: 8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5-(tetrahydro-pyran-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

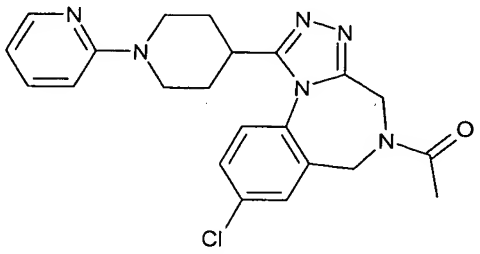


Tetrahydro-pyran-4-one (68 mg, 0.68 mmol) was added to a solution of the amine of example 4 (130 mg, 0.34 mmol) in dichloromethane (5ml). Mixture stirred at room temperature for 0.25hr before adding sodium triacetoxyborohydride (217mg, 1.0 mmol) and stirred for a further 18hr. Further Tetrahydro-pyran-4-one (68 mg, 0.68 mmol) and sodium triacetoxyborohydride (217mg, 1.0 mmol) were added and mixture heated to 40°C for 24hr. Reaction mixture was partitioned between 2N aqueous sodium carbonate solution (10ml) and ethyl acetate (50ml). The organic layer was washed three times with 2N aqueous sodium carbonate solution (10ml), once with saturated aqueous brine and dried over magnesium sulphate before filtering and evaporating the filtrate under reduced pressure. The residue was purified by chromatography on silica gel using a gradient of ethyl acetate in pentane (0% to 30%) as eluant followed by chromatography on silica gel using a gradient of methanol in dichloromethane (0% to 5%) as eluant to give the title compound as a brown foam (80 mg).

APCI MS *m/z* 465 $[MH]^+$, 487 $[MNa]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.57-175 (m, 4H), 1.75-2.20 (m, 6H), 2.72 (m, 1H), 2.98 (t, 2H), 3.16 (m, 1H), 3.39 (t, 2H), 3.40-3.60 (m, 2H), 3.60-4.10 (m, 2H), 4.02 (d, 2H), 4.34 (d, 2H), 6.61 (dd, 1H), 6.69 (d, 1H), 7.33 (d, 1H), 7.45-7.59 (m, 3H), 8.17 (d, 1H).

Example 8: 1-[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-ethanone dihydrochloride



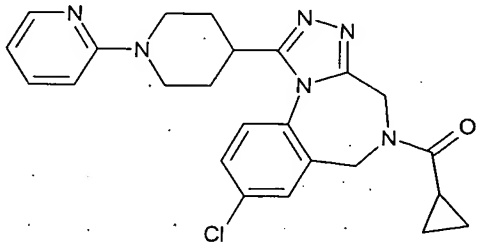
Acetyl chloride (0.1 ml, 1.4 mmol) was added to an ice cooled solution of the amine of example 4 (200 mg, 0.53 mmol) in dichloromethane (5ml) and stirred at room temperature for 20hr. Dichloromethane was evaporated off under reduced pressure and the residue purified by chromatography on silica gel using methanol in dichloromethane (5:95) as eluant. The residue was dissolved in dichloromethane (2ml) and hydrochloric acid (1M in diethyl ether, 2ml) added and solvents evaporated under reduced pressure to give the title compound as a brown foam (110 mg).

ESI MS *m/z* 423 $[M+H]^+$

^{1}H NMR (400MHz, CD_3OD): δ 1.95-2.40 (m, 7H, rotamers), 3.40-3.55 (m, 2H), 3.80 (m, 1H), 4.20-4.90 (m, 4H, rotamers), 4.82 (s, 2H), 7.02 (t, 1H), 7.46 (d, 1H), 7.80 (m, 1H), 7.91 (t, 1H), 7.95-8.00 (m, 2H), 8.07 (t, 1H)

Found C, 45.94%, H, 5.77%, N, 14.35%; $C_{22}H_{23}ClN_6O.2HCl.0.40CH_2Cl_2.3.07H_2O$ requires C, 45.98%, H, 5.50%, 14.36%

Example 9: [8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-cyclopropyl-methanone dihydrochloride

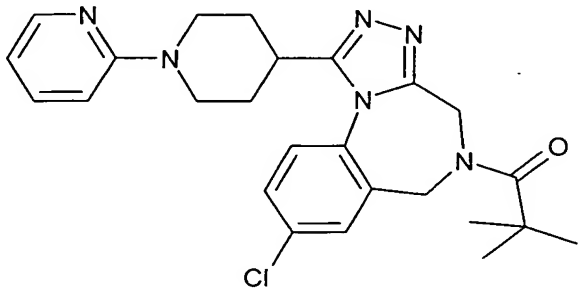


The title compound was prepared from Cyclopropanecarbonyl chloride and the amine of example 4, in 50% yield, using the procedure described in example 8.

ESI MS *m/z* 449 $[M+H]^+$

^{1}H NMR (400MHz, CD_3OD): δ 0.83-1.00 (m, 4H), 1.80-2.50 (m, 4H, rotamers), 3.40-3.60 (m, 2H), 3.89 (bt, 1H), 4.20-5.0 (m, 3H, rotamers), 4.86 (s, 2H), 7.04 (t, 1H), 7.26 (d, 1H), 7.82 (bd, 1H), 7.90-8.00 (m, 3H), 8.08 (t, 1H)

Example 10: 1-[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-2,2-dimethyl-propan-1-one dihydrochloride

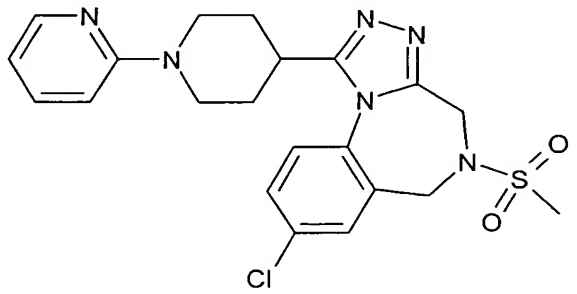


The title compound was prepared from 2,2-Dimethyl-propionyl chloride and the amine of example 4, in 54% yield, using the procedure described in example 8.

APCI MS *m/z* 465 $[M+H]^+$

^1H NMR (400MHz, CD_3OD): δ 1.40 (s, 9H), 1.80-2.60 (m, 4H, rotamers), 3.40-3.60 (m, 2H), 3.88 (bt, 1H), 4.10-5.00 (m, 4H, rotamers), 4.85 (s, 2H), 7.04 (t, 1H), 7.47 (d, 1H), 7.80-7.86 (m, 2H), 7.94 (d, 1H), 7.99 (d, 1H), 8.08 (t, 1H)

Example 11: 8-Chloro-5-methanesulfonyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

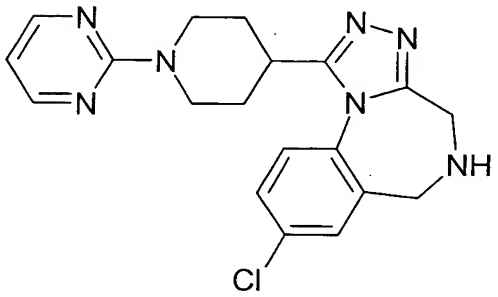


Methanesulfonyl chloride (0.1ml, 1.29 mmol) was added to an ice cooled solution of the amine of example 4 (200 mg, 0.53 mmol) in dichloromethane (5ml) and stirred at room temperature for 20hr. Dichloromethane was evaporated off under reduced pressure and the residue purified by chromatography on silica gel using methanol in dichloromethane (5:95) as eluant to give the title compound as a brown foam (71 mg).

APCI MS *m/z* 459 $[M+H]^+$, 481 $[M+Na]^+$

Found C, 52.98%, H, 5.05%, N, 17.20%; $C_{21}H_{23}ClN_6O_2S.0.25CH_2Cl_2$ requires C, 53.15%, H, 4.93%, 17.50%

Example 12: 8-Chloro-1-(1-pyrimidin-2-yl-piperidin-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene



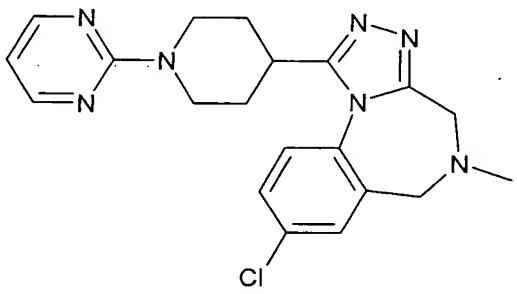
Toluene-4-sulfonic acid (5 mg, 0.03 mmol) was added to a solution of the oxadiazole of preparation 15 (2.34 g, 5.9 mmol) and heated to 140°C for 18hr. Mixture cooled and purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound (1.12 g) as an off white solid.

ESI MS *m/z* 382 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.60-2.20 (m, 4H), 2.95 (bt, 2H), 3.10 (m, 1H), 3.63 (s, 2H), 3.70-4.00 (m, 2H), 4.75 (d, 2H), 6.43 (t, 1H), 7.26 (d, 1H), 7.40-7.52 (m, 2H), 8.22 (d, 2H)

Found C, 57.24%, H, 5.31%, N, 24.10%; $C_{19}H_{20}ClN_7.0.25CH_2Cl_2$ requires C, 57.36%, H, 5.13%, 24.32%

Example 13: 8-Chloro-5-methyl-1-(1-pyrimidin-2-yl-piperidin-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene



Formaldehyde (37% w/v aqueous, 0.1 ml, 1.2 mmol) was added to a solution of the amine of example 12 (100 mg, 0.26 mmol) in dichloromethane (5ml). Mixture stirred at room temperature for 0.25hr before adding sodium triacetoxyborohydride (111mg, 0.53 mmol) and stirred for a further 18hr. Reaction mixture was partitioned between 2N aqueous sodium hydroxide solution (10ml) and dichloromethane (10ml). The organic layer was evaporated under reduced pressure and purified by chromatography on silica gel using

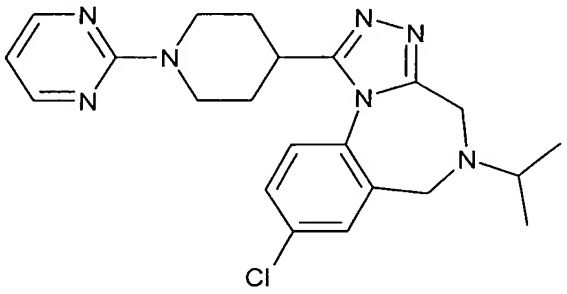
methanol in dichloromethane (5:95) as eluant to give the title compound as a brown foam (66 mg).

ESI MS *m/z* 382 $[M+Na]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.50-2.20 (m, 4H), 2.45 (s, 3H), 2.98 (bt, 2H), 3.10 (bt, 1H), 3.20-3.90 (m, 3H), 4.77 (s, 2H), 6.45 (s, 1H), 7.32 (d, 1H), 7.46-7.53 (m, 2H), 8.26 (d, 2H)

Found C, 59.12%, H, 5.50%, N, 24.00%; $C_{20}H_{22}ClN_7.0.15CH_2Cl_2$ requires C, 59.23%, H, 5.66%, N, 23.99%

Example 14: 8-Chloro-5-isopropyl-1-(1-pyrimidin-2-yl-piperidin-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene



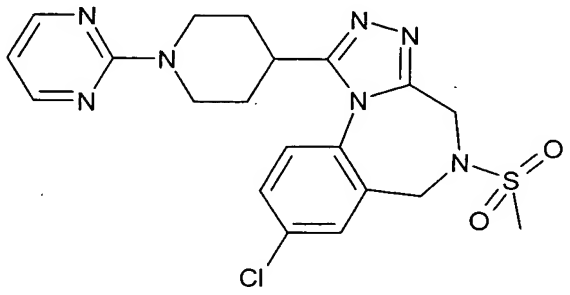
The title compound was prepared from acetone and the amine of example 12, in 65% yield, using the procedure described in example 13.

ESI MS *m/z* 382 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.20 (d, 6H), 1.60-2.10 (m, 4H), 2.90-3.07 (m, 3H), 3.18 (t, 1H), 3.30-4.00 (m, 4H), 4.78 (d, 2H), 6.47 (t, 1H), 7,29 (d, 1H), 7.48-7.58 (m, 2H), 8.30 (d, 2H)

Found C, 60.55%, H, 6.24%, N, 21.73%; $C_{22}H_{26}ClN_7.0.22CH_2Cl_2$ requires C, 60.17%, H, 6.03%, N, 22.11%.

Example 15: 8-Chloro-5-methanesulfonyl-1-(1-pyrimidin-2-yl-piperidin-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene

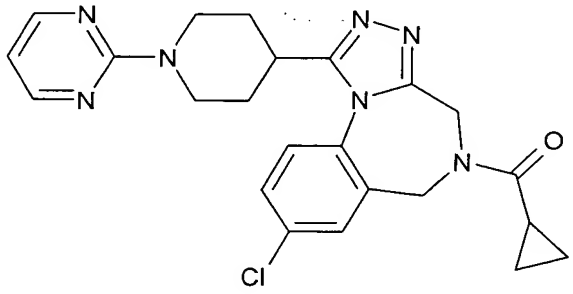


The title compound was prepared from the amine of example 12, in 69% yield, using the procedure described in example 11.

APCI MS *m/z* 460 $[M+H]^+$, 482 $[M+Na]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.40-2.40 (m, 6H), 2.95 (s, 3H), 2.90-4.20 (m, 5H), 4.40-5.30 (m, 4H), 6.52 (t, 1H), 7.40 (d, 1H), 7.60-7.70 (m, 2H), 8.32 (d, 2H)

Example 16: [8-Chloro-1- (1-pyrimidin-2-yl-piperidin-4-yl)-4H, 6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-cyclopropyl-methanone

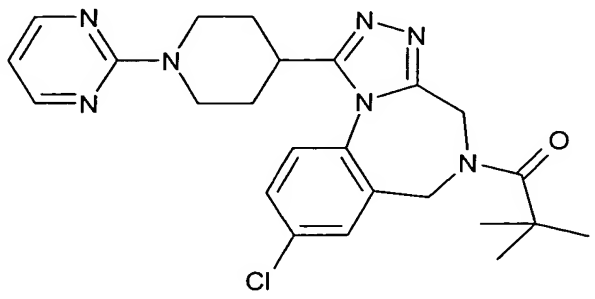


The title compound was prepared as an off white foam from cyclopropanecarbonyl chloride and the amine of example 12, in 69% yield, using the procedure described in example 3.

APCI MS *m/z* 472 $[M+Na]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 0.86 (m, 2H), 1.04 (m, 2H), 1.40-2.40 (m, 6H), 2.70-3.20 (m, 3H), 4.40-5.80 (m, 5H), 6.61 (t, 1H), 7.39 (d, 1H), 7.52-7.65 (m, 2H), 8.32 (d, 2H)

Example 17: 1-[8-Chloro-1-(1-pyrimidin-2-yl-piperidin-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-2,2-dimethyl-propan-1-one

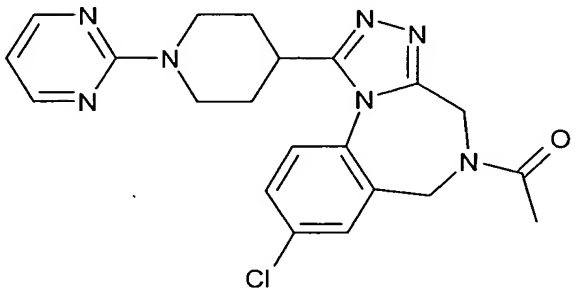


The title compound was prepared from 2,2-Dimethyl-propionyl chloride and the amine of example 12, in 42% yield, using the procedure described in example 3.

APCI MS *m/z* 466 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.38 (s, 9H), 1.40-2.40 (m, 7H), 2.90-3.10 (m, 2H), 3.17 (m, 1H), 4.60-5.00 (m, 2H), 5.27 (s, 2H), 6.58 (t, 1H), 7.35 (d, 1H), 7.54-7.68 (m, 2H), 8.29 (d, 1H)

Example 18: 1-[8-Chloro-1-(1-pyrimidin-2-yl-piperidin-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-ethanone

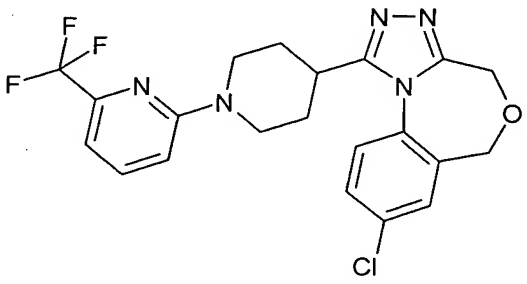


The title compound was prepared from acetyl chloride and the amine of example 12, in 37% yield, using the procedure described in example 3.

APCI MS *m/z* 424 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.40-2.50 (m, 10H), 2.70-3.30 (m, 4H), 4.70-4.90 (m, 2H), 6.52 (t, 1H), 7.38 (d, 1H), 7.54-7.64 (m, 2H), 8.33 (d, 2H)

Example 19: 8-Chloro-1-(6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene

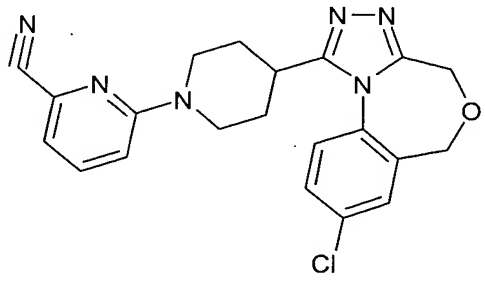


2-Chloro-6-trifluoromethyl-pyridine (55 mg, 0.30 mmol) and potassium carbonate (41 mg, 0.30 mmol) were added to a solution of the amine of preparation 29 (45 mg, 0.15 mmol) in N,N-dimethylformamide (2 ml). Mixture heated at 100°C for 18hr before evaporating under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound (30 mg), as a brown foam.

APCI MS *m/z* 450 $[M+H]^+$, 472 $[M+Na]^+$

^{1}H NMR (400MHz, CD_3OD): δ 1.88-2.06 (m, 4H), 3.01 (bt, 2H), 3.40 (m, 1H), 4.44 (bs, 2H), 4.51 (d, 2H), 4.59 (s, 2H), 6.94 (d, 1H), 7.02 (d, 1H), 7.68 (t, 1H), 7.74-7.78 (m, 4H).

Example 20: 4-(8-Chloro-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulen-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-carbonitrile



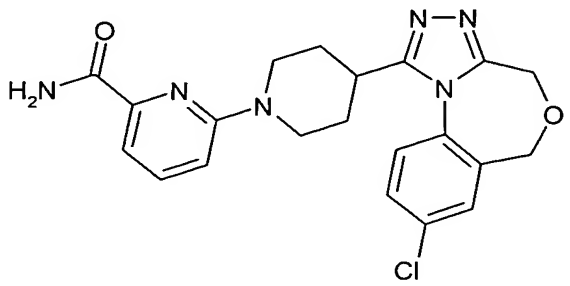
The title compound was prepared from 6-Chloro-pyridine-2-carbonitrile and the amine of preparation 29, in 61% yield, using the procedure described in example 19.

APCI MS *m/z* 407 $[M+H]^+$, 429 $[M+Na]^+$

^{1}H NMR (400MHz, CD_3OD): δ 1.86-2.08 (m, 4H), 3.03 (bt, 2H), 3.44 (m, 1H), 4.46 (m, 4H), 4.59 (s, 2H), 7.03 (d, 1H), 7.11 (d, 1H), 7.62 (dd, 1H), 7.72-7.78 (, 3H)

Found C, 61.31%, H, 4.73%, N, 20.38%; $C_{21}H_{19}ClN_6O.0.25H_2O$ requires C, 61.31%, H, 4.78%, N, 20.43%

Example 21: 4-(8-Chloro-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulen-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-carboxylic acid amide

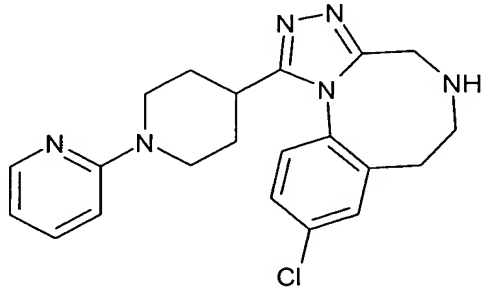


Powdered potassium hydroxide (46 mg, 81 mmol) was added to a solution of the carbonitrile of example 20 (110 mg, 0.27 mmol) in 2-Methyl-propan-2-ol (6 ml). The mixture was heated at 100°C for 18hr before evaporating under reduced pressure. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound (62 mg), as an off white solid.

APCI MS *m/z* 425 $[M+H]^+$, 447 $[M+Na]^+$

^{1}H NMR (400MHz, CD_3OD): δ 1.89-2.07 (m, 4H), 3.01 (bt, 2H), 3.42 (m ,1H), 4.45 (s, 2H), 4.52 (bd, 2H), 4.60 (s, 2H), 7.02 (d, 1H), 7.38 (d, 1H), 7.67 (dd, 1H), 7.72-7.78 (m, 4H)

Example 22: 13-Chloro-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-2,4,5,8-tetraaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene



Toluene-4-sulfonic acid (50 mg, 0.3 mmol) was added to a solution of the oxadiazole of preparation 41 (1.35 g, 3.3 mmol) and heated to 140°C for 2hr. Mixture cooled and purified by chromatography on silica gel using ethyl acetate followed by methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound (273 mg) as an off white solid.

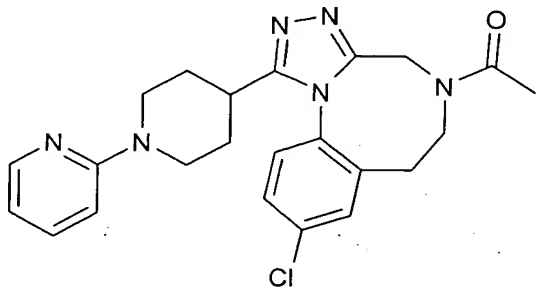
APCI MS *m/z* 398 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.42 (bd, 1H), 1.65 (dq, 1H), 2.05 (dt, 1H), 2.16 (bd, 1H), 2.32 (dq, 1H), 2.63-2.77 (m, 2H), 2.79-2.94 (m, 2H), 2.95 (m, 1H), 3.10 (d, 1H), 3.46 (dt,

1H), 4.18 (bd, 1H), 4.38 (bd, 1H), 4.41 (d, 1H), 6.59 (dd, 1H), 6.65 (d, 1H), 7.18 (d, 1H), 7.38-7.42 (m, 2H), 7.57 (t, 1H), 8.17 (d, 1H)

Found C, 62.41%, H, 5.98%, N, 20.45%; $C_{21}H_{23}ClN_6.0.12CH_2Cl_2$ requires C, 62.72%, H, 5.78%, N, 20.75%

Example 23: 1-[13-Chloro-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-2,4,5,8-tetraaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaen-8-yl]-ethanone



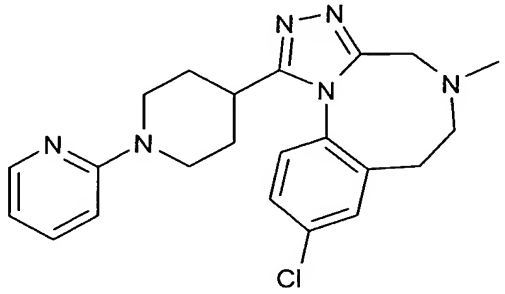
Acetic anhydride (35 □l, 0.37 mmol) was added to a solution of the amine of example 22 (120 mg, 0.30 mmol) and triethylamine in dichloromethane (5ml) and stirred at room temperature for 2hr. Dichloromethane was evaporated off under reduced pressure and the residue purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (5:0.5:95) as eluant to give the title compound as a white solid (120 mg).

APCI MS *m/z* 437 $[M+H]^+$, 459 $[M+Na]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.44 (bd, 1H), 1.63 (m, 1H), 2.16 (m, 2H), 2.10-2.22 (m, 2H), 2.28 (dt, 1H), 2.44 (s, 3H), 2.63-2.80 (m, 2H), 2.83-3.05 (m, 3H), 3.66 (d, 1H), 4.15 (bd, 1H), 4.41 (bd, 1H), 4.94 (dd, 1H), 5.06 (d, 1H), 6.59 (t, 1H), 6.63 (d, 1H), 7.17 (d, 1H), 7.38-7.50 (m, 3H), 8.14 (d, 1H)

Found C, 61.92%, H, 5.93%, N, 18.38%; $C_{21}H_{23}ClN_6.0.60H_2O$ requires C, 61.70, H, 5.90%, N, 18.77%

Example 24: 13-Chloro-8-methyl-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-2,4,5,8-tetraaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene

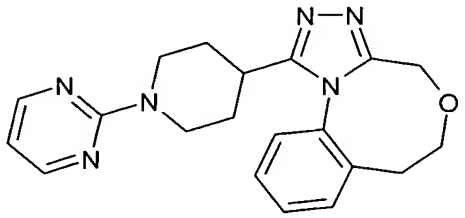


The title compound was prepared from the amine of example 22, in 78% yield, using the procedure described in example 2.

APCI MS *m/z* 409 $[M+H]^+$, 431 $[M+Na]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.41 (bd, 1H), 1.62 (dq, 1H), 2.14 (bd, 1H), 2.23-2.32 (m, 2H), 2.37 (s, 3H), 2.55 (dd, 1H), 2.66-2.78 (m, 2H), 2,88 (m, 1H), 2.96 (dt, 1H), 3.20 (d, 1H), 3.26 (dd, 1H), 4.15 (d, 2H), 4.35 (bd, 1H), 6.55 (dd, 1H), 6.62 (d, 1H), 7.14 (d, 1H), 7.32-7.39 (m, 2H), 7.41 (t, 1H), 8.12 (d, 1H)

Example 25: 3-(1-Pyrimidin-2-yl-piperidin-4-yl)-8-oxa-2,4,5-triaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene

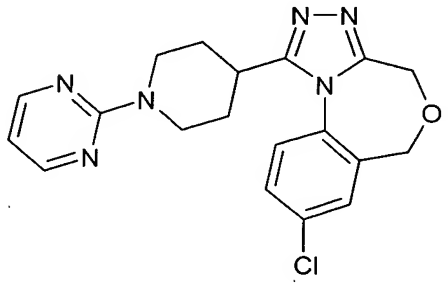


The title compound was prepared from the oxadiazole of preparation 24, in 50% yield, using the procedure described in example 22.

ESI MS *m/z* 364 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.48 (bd, 1H), 1.65 (dq, 1H), 2.20 (bd, 1H), 2.31 (dq, 1H), 2.44 (m, 1H), 2.83-2.95 (m, 2H), 3.01 (m, 1H), 3.11 (dt, 1H), 3.50 (q, 1H), 3.92 (d, 1H), 4.26 (m, 1H), 4.60 (d, 1H), 4.92 (d, 1H), 5.08 (d, 1H), 6.50 (t, 1H), 7.24 (t, 1H), 7.40 (t, 1H), 7.46 (d, 1H), 7.53 (t, 1H), 8.32 (d, 2H)

Example 26: 8-Chloro-1-(1-pyrimidin-2-yl-piperidin-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene

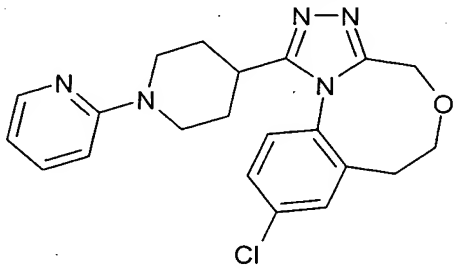


The title compound was prepared from the oxadiazole of preparation 23, in 70% yield, using the procedure described in example 22.

ESI MS *m/z* 383 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.92-2.13 (m, 4H), 3.07 (t, 2H), 3.12 (m, 1H), 4.39 (s, 2H), 4.66 (s, 2H), 4.82 (m, 2H), 6.53 (t, 1H), 7.39 (d, 1H), 7.57-7.63 (m, 2H), 8.33 (d, 2H)

Example 27: 13-Chloro-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-8-oxa-2,4,5-triaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene



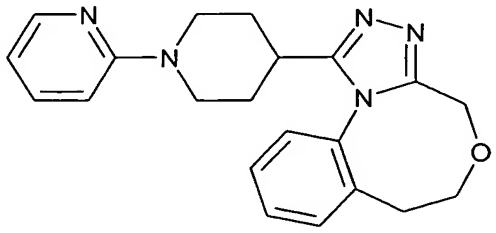
The title compound was prepared from the oxadiazole of preparation 22, in 40% yield, using the procedure described in example 22.

APCI MS *m/z* 396 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.44 (bd, 1H), 1.66 (dq, 1H), 2.17 (bd, 1H), 2.36 (dq, 1H), 2.43 (m, 1H), 2.72-2.85 (m, 2H), 2.89-3.03 (m, 2H), 3.55 (t, 1H), 3.97 (d, 1H), 4.14-4.26 (m, 2H), 4.40 (bd, 1H), 5.07 (d, 1H), 6.59 (dd, 1H), 6.64 (d, 1H), 7.19 (d, 1H), 7.38-7.48 (m, 3H), 8.15 (d, 1H)

Found C, 62.84%, H, 5.54%, N, 17.34%; $C_{21}H_{22}ClN_5O.0.08CH_2Cl_2$ requires C, 62.88%, H, 5.55%, N, 17.39%.

Example 28: 3-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-8-oxa-2,4,5-triaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene dihydrochloride

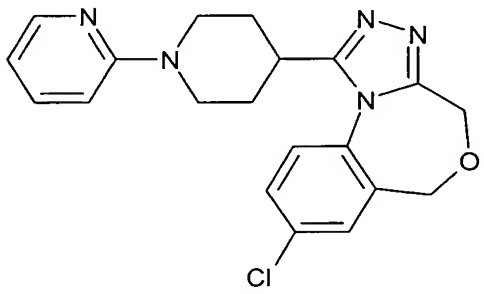


The title compound was prepared from the oxadiazole of preparation 21, in 49% yield, using the procedure described in example 22. Dihydrochloride salt was prepared using the procedure described in example 8.

APCI MS *m/z* 362 $[M+H]^+$

^{1}H NMR (400MHz, CD_3OD): δ 1.67-1.81 (m, 2H), 2.32 (dq, 1H), 2.47-2.57 (m, 2H), 3.11 (dd, 1H), 3.25 (dt, 1H), 3.33 (m, 2H), 3.45-3.62 (m, 3H), 4.07-4.16 (m, 2H), 4.30 (m, 1H), 4.40 (bd, 1H), 5.07 (d, 1H), 7.00 (t, 1H), 7.40 (d, 1H), 7.60-7.66 (m, 2H), 7.69-7.78 (m, 2H), 7.96 (d, 1H), 8.06 (t, 1H).

Example 29: 8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene



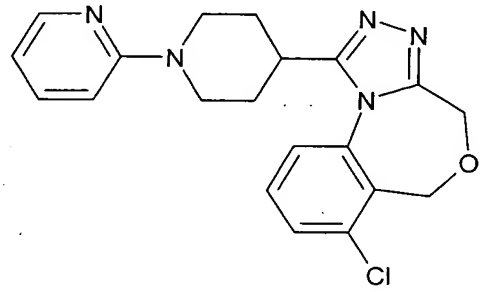
The title compound was prepared from the oxadiazole of preparation 20, in 60% yield, using the procedure described in example 22.

APCI MS *m/z* 382 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.97 (bd, 2H), 2.09 (m, 2H), 2.98 (dt, 2H), 3.17 (m, 1H), 4.32-4.40 (m, 4H), 4.64 (s, 2H), 6.59 (dd, 1H), 6.64 (d, 1H), 7.39 (d, 1H), 7.45 (t, 1H), 7.56-7.61 (m, 2H), 8.17 (d, 1H).

Found C, 60.19%, H, 5.17%, N, 17.31%; $C_{21}H_{22}ClN_5O.0.27CH_2Cl_2$ requires C, 60.14%, H, 5.11%, N, 17.30%

Example 30: 7-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene dihydrochloride

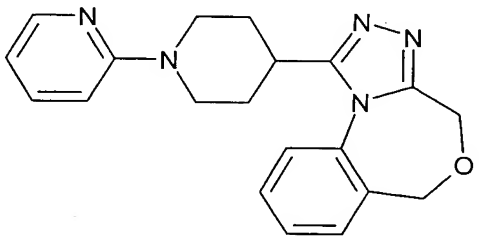


The title compound was prepared from the oxadiazole of preparation 17, in 21% yield, using the procedure described in example 22. Dihydrochloride salt was prepared using the procedure described in example 8.

APCI MS *m/z* 382 $[M+H]^+$

^1H NMR (400MHz, CD_3OD): δ 2.10 (m, 2H), 2.30 (m, 2H), 3.50 (bt, 2H), 3.74 (m, 1H), 4.32 (m, 2H), 4.93 (s, 2H), 7.00 (t, 1H), 7.46 (d, 1H), 7.77-7.95 (m, 3H), 8.00 (dd, 1H), 8.09 (t, 1H).

Example 31: 1-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene



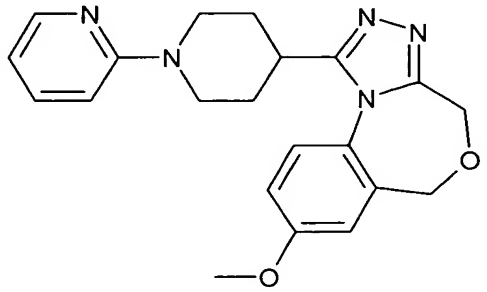
The title compound was prepared from the oxadiazole of preparation 16, in 41% yield, using the procedure described in example 22.

APCI MS *m/z* 348 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.98 (bd, 2H), 2.12 (m, 2H), 2.97 (t, 2H), 3.24 (m, 1H), 4.35 (d, 2H), 4.45 (s, 2H), 4.65 (s, 2H), 6.59 (dd, 1H), 6.69 (d, 1H), 7.38-7.49 (m, 2H), 7.53-7.65 (m, 3H), 8.18 (d, 1H)

Found C, 64.55%, H, 5.84%, N, 17.92%; $C_{20}H_{21}N_5O.0.40CH_2Cl_2.0.08C_8H_{10}$ requires C, 64.82%, H, 5.84%, N, 17.96%

Example 32: 8-Methoxy-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene dihydrochloride

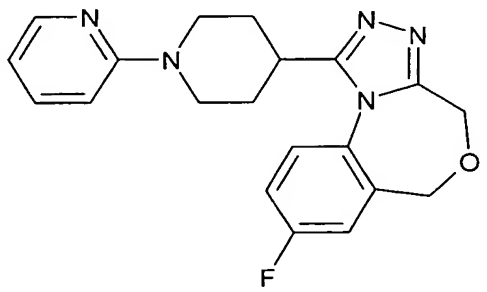


The title compound was prepared from the oxadiazole of preparation 19, in 68% yield, using the procedure described in example 22. Dihydrochloride salt was prepared using the procedure described in example 8.

ESI MS *m/z* 379 $[M+H]^+$

^1H NMR (400MHz, CD_3OD): δ 2.08 (bq, 2H), 2.30 (bd, 2H), 3.49 (t, 2H), 3.85 (m, 1H), 3.95 (s, 3H), 4.32 (bd, 2H), 4.59 (s, 2H), 4.68 (s, 2H), 7.03 (t, 1H), 7.31-7.35 (m, 2H), 7.45 (d, 1H), 7.80, (d, 1H), 7.97(d, 1H), 8.08 (t, 1H).

Example 33: 8-Fluoro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene



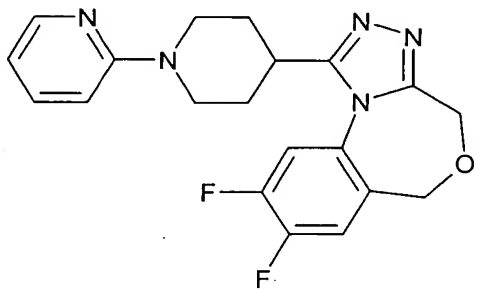
The title compound was prepared from the oxadiazole of preparation 31, in 62% yield, using the procedure described in example 22.

APCI MS *m/z* 366 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$): δ 1.90-2.16 (m, 4H), 2.97 (dt, 2H), 3.16 (m, 1H), 4.28-4.40 (m, 4H), 4.63 (s, 2H), 6.58 (dd, 1H), 6.66 (d, 1H), 7.24-7.35 (m, 2H), 7.40-7.52 (m, 2H), 8.15 (d, 1H)

Found C, 64.47%, H, 5.56%, N, 18.50%; $C_{20}H_{20}FN_5O.0.07CH_2Cl_2.0.07EtOAc$ requires C, 64.74%, H, 5.53%, N, 18.55%.

Example 34: 8,9-Difluoro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene dihydrochloride



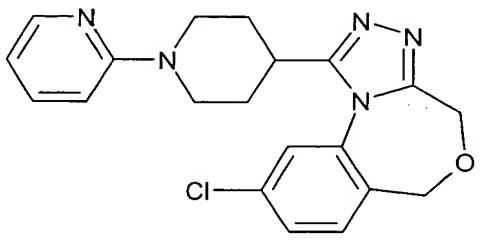
The title compound was prepared from the oxadiazole of preparation 33, in 44% yield, using the procedure described in example 22. Dihydrochloride salt was prepared using the procedure described in example 8.

APCI MS *m/z* 384 $[M+H]^+$

^{1}H NMR (400MHz, CD_3OD): δ 2.00-2.13 (m, 2H), 2.18-2.37 (m, 2H), 3.52 (dt, 2H), 4.33 (bd, 2H), 4.58 (s, 2H), 4.68 (s, 2H), 7.02 (t, 1H), 7.47 (d, 1H), 7.81 (dd, 1H), 7.94-8.02 (m, 2H), 8.06 (t, 1H)

Found C, 49.58%, H, 5.01%, N, 14.25%; $C_{20}H_{19}F_2N_5O_1.2HCl.0.30CH_2Cl_2.0.58H_2O$ requires C, 49.53%, H, 4.66%, N, 14.23%

Example 35: 9-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene dihydrochloride

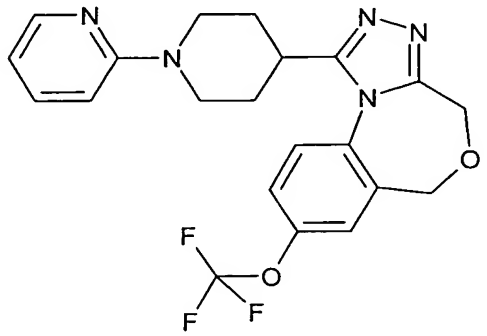


The title compound was prepared from the oxadiazole of preparation 18, in 54% yield, using the procedure described in example 22. Dihydrochloride salt was prepared using the procedure described in example 8.

APCI MS *m/z* 383 $[M+H]^+$

^{1}H NMR (400MHz, CD_3OD): δ 2.10 (m, 2H), 2.35 (m, 2H), 3.55 (dt, 2H), 4.00 (bd, 1H), 4.35 (m, 2H), 4.65 (s, 2H), 4.80 (s, 2H), 7.02 (m, 1H), 7.45 (m, 1H), 7.81 (s, 2H), 8.00 (m, 3H)

Example 36: 1-(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-8-trifluoromethoxy-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene



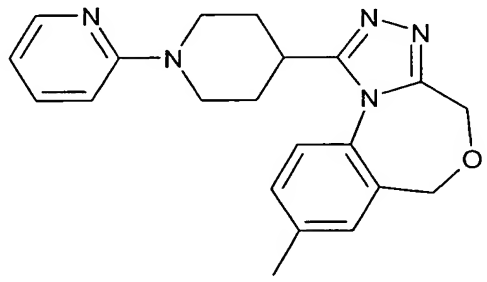
The title compound was prepared from the oxadiazole of preparation 36, in 44% yield, using the procedure described in example 22.

APCI MS *m/z* 432 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.99 (m, 2H), 2.13 (m, 2H), 3.00 (dt, 2H), 3.17 (m, 1H), 4.37 (d, 2H), 4.42 (s, 2H), 4.66 (s, 2H), 6.60 (dd, 1H), 6.68 (d, 1H), 7.40-7.52 (m, 4H), 8.16 (d, 1H)

Found C, 58.16%, H, 4.77%, N, 15.84%; $C_{21}H_{20}F_3N_5O_2$ requires C, 58.47%, H, 4.67%, N, 16.23%

Example 37: 8-Methyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-5-oxa-2,3,10b-triaza-benzo[e]azulene

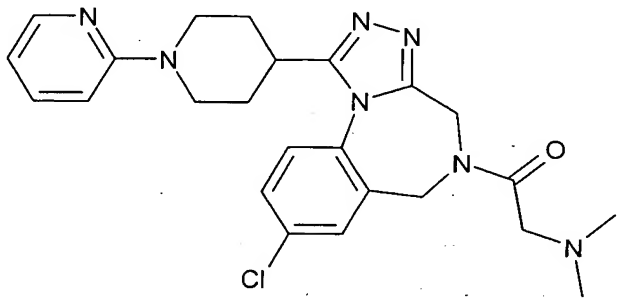


The title compound was prepared from the oxadiazole of preparation 37, in 48% yield, using the procedure described in example 22.

APCI MS *m/z* 362 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$): δ 1.99 (m, 4H), 2.43 (m, 3H), 2.96 (dt, 2H), 3.41 (m, 1H), 4.34 (d, 2H), 4.42 (s, 2H), 4.66 (brs, 2H), 6.62 (dd, 1H), 6.83 (d, 1H), 7.44-7.60 (m, 3H), 7.63 (d, 1H), 8.06 (d, 1H)

Example 38: 1-[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-2-dimethylamino-ethanone



A solution of HBTU (152 mg, 0.38 mmol) in N,N-dimethylacetamide (1.9 ml) was added to a solution of the amine of example 4 (97 mg, 0.26 mmol), triethylamine (1.5 □l, cat.) and dimethylamino-acetic acid (36 mg, 0.26 mmol) in N,N-dimethylacetamide (2.5 ml) and heated to 50°C for 2hr. Mixture cooled and solvent evaporated under reduced pressure. Residue was partition between dichloromethane (10ml) and 2M aqueous sodium hydroxide solution (10ml). Organic phase was dried over magnesium sulphate before being evaporated under reduced pressure and purified by chromatography on silica gel using methanol and ammonium hydroxide in dichloromethane (7:1:93) as eluant to give the title compound (70 mg) as a brown foam.

APCI MS *m/z* 466 $[M+H]^+$

Found C, 60.14%, H, 5.93%, N, 20.29%; $C_{24}H_{28}ClN_7O.2HCl.0.20CH_2Cl_2$ requires C, 60.18%, H, 5.93%, N, 20.30%

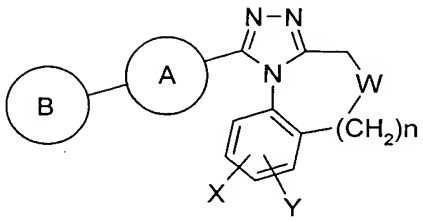
Example 39:

Examples of specific compounds, tested in screen 1.0 (V_{1A} filter binding assay) as described above, are illustrated in the table below

Example No.	Ki (nM)
5	4.66
6	2.37
8	2.47
9	1.21
11	0.68
22	1.32
24	1.00
27	1.25

CLAIMS:

1. A compound of formula **(I)**,



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

W is O, S, or NR^1

R^1 represents H, C_{1-6} alkyl, $-(CH_2)_a-[C_{3-8}$ cycloalkyl], phenyl, benzyl, pyridyl, pyrimidyl, $-COR^2$, $-CO_2R^2$, $-CO-(CH_2)_a-NR^2R^3$, $-SO_2R^2$, $-(CH_2)_b-OR^2$, $-(CH_2)_b-NR^2R^3$, or a saturated heterocycle of from 3 to 8 atoms containing one or more heteroatoms selected from O, N and S;

X and Y independently represent H, halogen, OH, CF_3, OCF_3, R^4, $-(CH_2)_d-CONR^4R^5$, $-(CH_2)_d-CN$, $-(CH_2)_d-SO_2NR^4R^5$, $-(CH_2)_d-NR^4SO_2Me$, $-(CH_2)_d-COR^4$, $-(CH_2)_d-OCOR^4$, $-(CH_2)_d-NHCOR^4$, $-(CH_2)_d-NR^4COR^5$, $-(CH_2)_d-OR^6$ or $-(CH_2)_d-CO_2R^6$;

Ring **A** represents a piperidinyl, piperazinyl, pyrrolidinyl or azetidinyl group;

Ring **B** represents a phenyl, pyridinyl or pyrimidinyl group (optionally substituted with one or more groups independently selected from halogen, CN, $CONH_2$, CF_3, OCF_3, R^7, and $-(CH_2)_f-OR^8$);

R^2, R^3, R^4, $R^5$and R^7 independently represent H, straight or branched C_{1-6} alkyl, $-(CH_2)_c-[C_{3-8}$ cycloalkyl], phenyl, benzyl, pyridyl or pyrimidyl;
or R^2 and R^3, or R^4 and R^5, together with the nitrogen atom to which they are attached independently represent a heterocycle of from 3 to 8 atoms;

R^6 and R^8 independently represent H, straight or branched C_{1-6} alkyl, $-(CH_2)_c-[C_{3-8}$ cycloalkyl], $-(CH_2)_e-NR^4R^5$, $-(CH_2)_e-OR^4$, phenyl, benzyl, pyridyl or pyrimidyl;

n = 0, 1 or 2;

a , c, d and f are each independently selected from 0, 1, 2 and 3;
b and e are each independently selected from 2 and 3.

2. A compound according to claim 1, wherein W represents NR^1 or O.

3. A compound according to claim 1 or claim 2, wherein R^1 represents H, $-COR^2$, $-CO-(CH_2)_a-NR^2R^3$ or $-SO_2R^2$.

4. A compound according to any preceding claim, wherein R^2 represents C_{1-6} alkyl or $-(CH_2)_c-[C_{3-8}$ cycloalkyl];

5. A compound according to any preceding claim, wherein R^3 represents C_{1-6} alkyl.

6. A compound according to any preceding claim, wherein X is H.

7. A compound according to any preceding claim, wherein Y is in the para-position of the aromatic ring to which it is attached in relation to the triazole ring.

8. A compound according to any preceding claim, wherein Y represents halogen.

9. A compound according to any preceding claim, wherein ring A represents piperidinyl or piperazinyl.

10. A compound according to any preceding claim, wherein ring B represents pyridinyl, pyrimidinyl or phenyl.

11. A compound according to claim 1, selected from:
8-Chloro-5-methyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene trihydrochloride;
8-Chloro-5-isopropyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene trihydrochloride;
1-[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-ethanone dihydrochloride;

[8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulen-5-yl]-cyclopropyl-methanone dihydrochloride;

8-Chloro-5-methanesulfonyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene;

13-Chloro-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-2,4,5,8-tetraaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene;

13-Chloro-8-methyl-3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-2,4,5,8-tetraaza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),3,5,12,14-pentaene; and

4-[5-(2-Amino-5-chloro-benzyloxymethyl)-[1,3,4]oxadiazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester, or pharmaceutically acceptable salts or solvates thereof.

12. The use of a compound according to any of claims 1 to 11 as a medicament.

13. A method of treatment of aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male or female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection or urolithiasis, comprising administering a therapeutically effective amount of a compound according to any of claims 1 to 11 to a patient suffering from such a disorder.

14. A method according to claim 13, wherein the disorder is dysmenorrhoea.

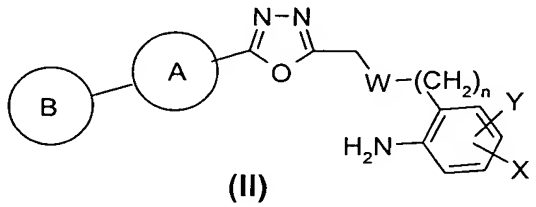
15. The use of a compound according to any of claims 1 to 11 in the manufacture of a medicament for the treatment of aggression, Alzheimer's disease, anorexia nervosa, anxiety disorder, asthma, atherosclerosis, cardiac failure, cardiovascular disease, cataract, central nervous system disease, cerebrovascular ischemia, cirrhosis, cognitive disorder, Cushing's disease, depression, diabetes mellitus, dysmenorrhoea, edema, emesis, endometriosis, gastrointestinal disease, glaucoma, gynaecological disease, heart disease, hypertension, hyponatremia, ischemia, ischemic heart disease, lung tumor, micturition disorder, motion sickness, neoplasm, nephrotoxicity, non-insulin dependent

diabetes, obesity, obsessive/compulsive disorder, ocular hypertension, premature labor, pulmonary disease, Raynaud's disease, renal disease, renal failure, male or female sexual dysfunction, sleep disorder, spinal cord injury, thrombosis, urogenital tract infection or urolithiasis.

16. Use according to claim 15, for the treatment of dysmenorrhoea.

17. A pharmaceutical formulation including a compound according to any of claims 1 to 11, together with a pharmaceutically acceptable excipient, diluent or carrier.

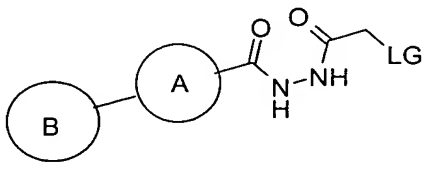
18. An intermediate of formula **(II)**:



(II)

wherein X, Y, W, rings **A** and **B**, and n are as defined in claim 1.

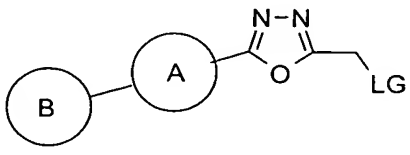
19. An intermediate of formula **(XV)**:



(XV)

wherein rings **A** and **B** are as defined in claim 1 and LG represents a suitable leaving group.

20. An intermediate of formula **(X)**:



(X)

wherein rings **A** and **B** are as defined in claim 1 and LG represents a suitable leaving group.